JUL 1 8 1978
NCI/ICRDB/OK-78/02

HE 20.3773/3:OK-78/02
NTISUB/D/229-003

ONCOLOGY OVERVIEW

COMPLETED
ORIGINAL

SELECTED ABSTRACTS

ON

THE ROLE OF DIETARY FAT IN CARCINOGENESIS

SEPTEMBER 26, 1978

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service • National Institutes of Health •
National Cancer Institute

A SERVICE OF THE
INTERNATIONAL CANCER RESEARCH DATA BANK (ICRDB)

49

Oncology Overviews are a service of the International Cancer Research Data Bank (ICRDB) program of the National Cancer Institute. Each *Oncology Overview* represents a survey of the literature associated with a selected area of cancer research. It contains abstracts of articles which have been selected and organized by researchers associated with the field. The purpose of this *Oncology Overview* is to facilitate and promote the exchange of information between cancer scientists by keeping them aware of literature related to their research being published by other laboratories throughout the world.

The material published in *Oncology Overviews* is obtained from Cancerline, an online cancer information system created by the ICRDB program in cooperation with the National Library of Medicine. Abstracts from the Cancerline data base, which is updated monthly with new articles abstracted from more than 1500 journals, can be retrieved via online computer terminals at more than 500 locations in the U.S. and other countries. Any organization linked to the Medlars Medline system at the National Library of Medicine has access to the Cancerline data base.

This *Oncology Overview* is sent automatically to researchers in the subject area who are identified on the basis of current research project descriptions submitted to an ICRDB-supported Current Cancer Research Project Analysis Center (CCRESPAC). We encourage all cancer researchers to provide a complete and current project description to CCRESPAC. If you have not recently supplied such a description to an agency providing input to this program (ie, NIH, American Cancer Society, Cancer Center Directors, etc.), you may obtain forms and additonal information about data input from the ICRDB program office address listed below.

Oncology Overviews may also be obtained by any requestor at modest cost from the National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, Virginia 22161, USA.

This *Oncology Overview* is prepared for the ICRDB program by the Cancer Information Dissemination and Analysis Center (CIDAC) for Carcinogenesis Information. Future *Overview* editions depend on user needs and satisfaction. If you have favorable comments on this *Oncology Overview*, or you would like to receive other ICRDB publications and learn about other ICRDB information services, please contact:

ICRDB Program Office
National Cancer Institute
Blair Building, Room 114
8300 Colesville Road
Silver Spring, Maryland 20910, USA

EACH RESEARCHER RECEIVING THIS PUBLICATION IS URGED TO CIRCULATE THIS *OVERVIEW* TO COLLEAGUES, CO-WORKERS, AND OTHERS WHO ARE ENGAGED IN PROJECTS RELATED TO THE AREA COVERED BY THIS PUBLICATION.

TABLE OF CONTENTS

	ABSTRACT NUMBER
INTRODUCTION	
EDITORIAL COMMENTARY	
I. ASSOCIATION OF FATS WITH SPECIFIC HUMAN CANCERS	
A. Dietary Fat and GI Cancer	1-24
B. Dietary Fat and/or Obesity and Breast Cancer	25-36
C. Obesity and Endometrial Cancer	37-43
D. Fat and Cancer of Multiple or Miscellaneous Sites	44-53
II. NUTRITIONAL ASPECTS OF HUMAN CANCER INCIDENCE	
A. Nutritional Studies Including Fat and General Cancer Incidence	54-74
B. Specific Dietary Studies in Humans	75-78
III. CARCINOGENS ASSOCIATED WITH FOOD LIPIDS	
A. Aflatoxin and Other Natural Contaminating Carcinogens in Lipids	79-87
B. Environmental Carcinogenic Pollutants in Lipids	88-93
C. Carcinogenic Activity Resulting from Food Processing	94-103
IV. EXPERIMENTAL STUDIES CONCERNING LIPIDS AND FATTY ACIDS	
A. Induction of Tumors with Dietary Lipids	104-109
B. Induction of Tumors with Fatty Acids	110-113
C. Modification of Chemical Carcinogenesis by Lipids and Fatty Acids	114-144
D. Influence of Liprotropic Deficiency on Tumor Growth and Induction	145-158
E. Distribution of Lipids and Fatty Acids in Neoplastic Tissues or Cells	159-168
F. Studies with Lipid Peroxides	169-175
G. Biochemical and Other Studies Concerning Lipids	176-180
SUBJECT INDEX	
AUTHOR INDEX	

INTRODUCTION

This ONCOLOGY OVERVIEW on fat carcinogenesis is comprised of abstracts of articles published in 1970-1977 (with some dating back to 1963) that exist in the CANCERLINE computerized data base. The strategy used for the on-line data base is available on request from the CIDAC and can be entered at any MEDLARS/MEDLINE terminal system in order to update the references in this area.

The scope of this OVERVIEW covers all aspects of the carcinogenicity and influences on carcinogenicity by fats and fatty acids. Included are the epidemiological association of high-fat diets and obesity with various cancers, carcinogenicity of lipid soluble chemicals and pollutants, and carcinogenicity related to lipid alteration during food processing. Experimental studies covering induction of cancer with lipids and fatty acids, modification of chemical carcinogenesis by lipids, role of lipotropes in cancer induction, and various bicchemical studies involving lipids are also included.

This OVERVIEW was prepared by Leon S. Vann (editor), John S. Krebs, William E. Davis, Jr., and Barbara Thompson of the CIDAC staff, SRI International, 333 Ravenswood Avenue, Menlo Park, California 94025.

EDITORIAL COMMENTARY

Various studies have indicated that certain relationships exist between dietary lipids and carcinogenesis. The papers abstracted in this OVERVIEW describe some of these relationships.

Epidemiological studies have shown that the incidence of cancer of the colon and rectum is increased among populations whose diets are high in animal fats (Section I.A.). Possible reasons for this increased cancer risk are that the increased secretion of bile acids induced by ingestion of high amounts of fat causes changes in anaerobic intestinal flora and the metabolic formation of carcinogens. Furthermore, fat slows the transit of food through the GI tract, increasing the contact time of any carcinogens with the lining of the intestine.

The incidence of breast cancer appears to be higher among women ingesting large amounts of fats and among obese women in general (Section I.B.). Increased secretion of prolactin and estrogen may occur as a result of high fat ingestion and obesity, and the increased secretion as well as changes in the relative ratios of these hormones in the circulation are thought to render mammary tissues more susceptible to neoplastic changes. Some evidence exists for an increased incidence of uterine cancer (Section I.C.), which is also attributed to hormonal changes as well as to the absorption from the GI tract of estrogenic types of compounds that result from the metabolism of the increased cholesterol and bile acids associated with high-fat diets.

Ingestion of diets high in lipids may initiate neoplastic changes more directly in that many carcinogenic chemicals are lipid soluble and hence are more likely to be present in foods of high fat content (Section III.). High fat solubility is a property of many natural carcinogens such as aflatoxins, other mycotoxins, safrole, and some carcinogenic alkaloids. Many synthetic pesticides such as the chlorohydrocarbons, some of which are known carcinogens, are also fat soluble.

Controlled experiments (Section IV.) have shown that when known chemical carcinogens - each tending to be specific for a given type of cancer in a laboratory animal - are incorporated into high-fat diets, the incidence of cancer development is increased. Other experiments have shown that modifications of lipid metabolism can result in the formation of carcinogenic derivatives from various lipids, and this has been most clearly demonstrated in the formation of various lipid peroxides. Moreover, other research has shown that certain 'trace' nutrients - vitamins, lipotropic compounds, and antioxidants - involved in lipid metabolism will, when present in adequate amounts in the diet, prevent the formation of some of the fat derivatives that appear to have carcinogenic actions. Among such nutrients are choline, methionine, selenium, and vitamins A and C.

I. ASSOCIATION OF FATS WITH SPECIFIC HUMAN CANCERS

A. Dietary Fat and GI Cancer

1. DIETARY FAT AND COLON CANCER.

Wynder EL, Reddy BS
Am. Health Found., New York, N.Y.
J Natl Cancer Inst; 54(1):7-10 1975

An association between cancer of the colon and dietary animal fat and/or cholesterol is suggested by the geographic and socioeconomic distribution of colon cancer, data on migrant populations, and retrospective studies of U.S and Japanese patients with large-bowel cancer. The rate of colon cancer, particularly in the sigmoid region, in Japanese immigrants increases significantly as they adjust to American diets. This increase may be related to intake of beef, which contributes 35-45% of the total fat content of the American diet. Intrarectal instillation of two bile acids (deoxycholic and lithocholic acid) in rats significantly promoted the development of N-methyl-N'-nitro- N-nitrosoguanidine - induced adenomas. Parallel studies in vitro indicated that these bile acids were more extensively degraded to microbial products by anaerobes isolated from Americans on a mixed Western diet than from American vegetarians. These data support the concept that different diets lead to typical microflora populations which control the metabolism of intraluminal compounds. One or a combination of active anaerobic strains, acting simultaneously or sequentially on cholesterol or bile acid metabolites or degradation products, could possibly form a cocarcinogen and/or a carcinogen. (34 refs)

2. DIET AND METABOLISM: LARGE-BOWEL CANCER.

Reddy BS, Mastromarino A, Wynder E
Naylor Dana Inst for Disease Prevention, American Health Foundation, Valhalla, NY 10595
Cancer Suppl; 39(4):1815-1819 1977

Epidemiological data demonstrate that colon cancer incidence is associated mainly with high dietary fat consumption. Studies in metabolic epidemiology indicate that high fat intake influences both the amount and type of bile acids and neutral sterols and intestinal microflora acting on these compounds which may contain tumorigenic activity for the colon. This is compatible with the results of studies comparing populations with high or low risk for the colon cancer and patients with colon cancer. (33 Refs) (Author Abstract)

3. ENVIRONMENTAL FACTORS OF CANCER OF THE COLON AND RECTUM. II. JAPANESE EPIDEMIOLOGICAL DATA.

Wynder EL, Kajitani T, Ishikawa S, Dodo H, Takano A
Sloan-Kettering Inst. Cancer Res., New York, N. Y.
Cancer; 23(5):1210-1220 1969

Cancer of the large intestine caused 4.9% of all cancer deaths in Japan in 1965. Cancer of the colon is significantly less frequent in Japan than in the U.S. (although the mortality rate in Japan may be increasing), whereas cancer of the rectum (with a stable mortality rate in Japan) is about equally frequent in Japan and in the U.S white population. An interview survey of 107 Japanese patients with cancer of the colon or rectum and 307 control subjects was conducted, to detect the influence of environmental factors. The patients with cancer of the rectum were not significantly different from the controls in any of the parameters studied, including dietary habits (the patients were asked about their consumption of smoked, salted or charcoal-broiled meat and fish, among other foods). The patients with cancer of the colon tended to be of higher socioeconomic status than the patients with cancer of the rectum or the controls, and reported a diet with more milk and fruit and less rice than the usual Japanese diet. The cancer patients were not significantly different from the controls with respect to medical or surgical histories, body wt, serum cholesterol levels, smoking, or alcohol consumption. It is suggested that dietary fat, by affecting the composition of the intestinal flora, may influence the pathogenesis of cancer of the colon.

4. DIET AND CANCER.

Gori GB
Div. Cancer Cause and Prevention, NCI, NIH, Bethesda, MD 20014
J Am Diet Assoc; 71(4):375-379 1977

Diet may play an important role in the etiology of cancer in two ways: through ingestion of carcinogens or substances that are metabolized to carcinogens, or by establishing a condition that modulates organ susceptibility and response to cancer-causing agents. Particular emphasis is placed on the association between fat intake and bowel cancer. Incidence and mortality data from the literature are reviewed. (36 Refs)

5. DIET AND DISEASES OF THE COLON.

Thompson TF
La Paz, Bolivia
JAMA; 235(26):2815 1976

The author presents clinical observations that support the hypothesis that diets with high fat and low fiber levels play a role in diseases such as cancer of the intestine, adenomatous polyps, ulcerative colitis, diverticulitis, and large-vessel arteriosclerosis. These diseases are rare in La Paz, Bolivia (where the author, a surgeon, works), similar to other underdeveloped regions where refined foods and high-fat diets are not known. In another observation, he states that the increase in diverticulitis (also rare in La Paz, one case in 12 yr) in the United States is probably a result of changes in diet patterns over the last four decades. (3 refs)

6. BACTERIA AND THE ETIOLOGY OF COLONIC CANCER.

Hill MJ
Bact. Metab. Res. Lab., London, England
Cancer Suppl; 34(3):815-818 1974

It is postulated that intestinal bacterial flora produce colonic carcinogens or cocarcinogens from bile acids, the concentrations of which are ultimately influenced by the amount of intake of dietary fat. In support of this hypothesis is the fact that full aromatization of the bile acid nucleus yields a cyclopentophenanthrene which has been shown to be carcinogenic. All four types of nuclear dehydrogenation reactions necessary to achieve full aromatization of bile acids have been demonstrated using human gut bacteria and three of these reactions are carried out almost exclusively by a group of clostridia related to Clostridium paraputrificum (NDH

(nuclear dehydrogenating) clostridia). Analysis of nine world populations differing in their incidence of colonic carcinoma showed a positive correlation between a high cancer rate and fecal bile acid concentration, the degree of bile acid degradation, fecal neutral steroid concentration and degradation, the presence of intestinal flora capable of aromatizing bile, total fecal acid steroid concentration and, fecal dihydroxycholanic acid concentration. Higher income groups within a given population showed both increased colonic cancer rates and increased fecal acid steroid degradation compared to lower income groups. Eighteen of 22 large bowel carcinoma patients had both more than 6 mg/g dry wt bile acids and more than 103 NDH clostridia/g wet wt of feces compared to only one of 51 controls with intestinal diseases other than cancer.

7. LARGE-BOWEL CANCER IN HAWAIIAN JAPANESE.

Haenszel W, Berg JW, Segi M, Kurihara M, Locke FB
Natl. Cancer Inst., Bethesda, Md.
J Natl Cancer Inst; 51(6):1765-1779 1973

Study of 179 Japanese patients with bowel cancer and 357 hospital controls in Hawaii revealed excess risks for persons who regularly ate Western-style meals only. The similarity in findings for Issei and Nisei sharply contrasts with results previously reported for stomach cancer in Issei and Nisei, where the reduced risk among persons regularly eating Western-style meals only was limited to the second-generation Nisei. Bowel cancer was associated with consumption of specific foods. Bowel cancer patients ate meats, legumes, and starches more frequently, with the case-control disparity being less pronounced for individuals consuming starches than for those eating meat and legumes. Beef and string beans were the major contributors to the meat and legume effects. There seemed to be separate effects for beef, string beans, and starches, and the case-control contrasts were strengthened when various combinations of foods were considered. Points of consistency between the Hawaii study and other evidence are noted. The findings on beef may narrow the area of search for etiologic factors. Beef is higher in saturated fats than other sources of animal protein, such as chicken, pork, and fish, and attention might be directed to mechanisms involving the direct action of saturated fatty acids or indirectly via bile metabolites and their cholesterol precursors.

8. POSSIBILITIES FOR PREVENTION OF LARGE BOWEL CANCER. (PP. 143-151)

Williams RE, Hill MJ, Drasar BS
Fundamentals in Cancer Prevention, Proceedings of the 6th International Symposium of the Princess Takamatsu Cancer Research Fund, Tokyo, 1975. Princess Takamatsu Symposium Tokyo, 1976.

Statistical studies are cited that attribute a high incidence of large bowel cancer to a high dietary consumption of meats and fats, which affect the substrates available to the gut bacteria and the bacterial species present. The major factor in the etiology of this disease might be the production of a carcinogen or cocarcinogen from bile acids by the gut microflora (Clostridia, Bacteroides). Clostridium paraputrificans, C. tertium and C. indolis produce a partially desaturated acid steroid by dehydrogenation of bile steroids. Preventive measures proposed were: reduction of steroids reaching the gut; reduction of bacterial action on the steroids; and protection of the colon mucosa. A study was proposed to ascertain if high levels of acid steroids, or large numbers of Clostridia containing dehydrogenating enzymes in the feces of healthy individuals might be used as a screening method to detect the development of large bowel cancer. (19 Refs)

9. LARGE BOWEL CANCER: CAUSATION AND MANAGEMENT.

McIllMurray MB, Langman MJ
City Hosp., Nottingham, England
Gut; 16(10):815-820 1975

The causes and management of large bowel cancer are reviewed. Comparisons of diets and social characterisitcs of colonic cancer patients and matched controls have been performed. Proportions of animal protein and fat correlate well with incidence of large bowel cancer: increased fat consumption parallels an increased cancer incidence. Supporting these findings is the correlation between colonic cancer and coronary disease. Animal protein intake is also positively correlated with colonic cancer. An explanation may be that dietary constituents influence the microbial flora of the gut and/or intestinal secretory patterns. The use of carcinoembryonic antigen (CEA) is disappointing in its application as a diagnostic test. The ability for cancer patients to develop an immune response to tumors is studied in vivo and in vitro. Promising preliminary studies show specific inhibition of adherence after exposing peripheral blood leukocytes from patients with colonic cancer to colonic cancer extracts but this has still to be confirmed on a larger scale. Prospects for improving treatment by nonsurgical means remain vague. Available chemotherapeutic agents are largely ineffective and there is no evidence that adjuvant immunotherapy will be clinically useful. (57 refs)

10. DISTRIBUTION OF SMALL BOWEL TUMORS.

Lowenfels AB, Sonni A
Div. Surgery, Westchester County Medical Center, Valhalla, NY 10595
Cancer Lett (Amsterdam); 3(1/2):83-86 1977

The anatomic distribution of 784 tumors of the small intestine was studied, and epidemiological data analyzed to determine the relation of these rare cancers to other gastrointestinal tumors and to diet. The anatomic distribution of cancer of the small intestine is unusual. Most tumors occur in the duodenum or proximal jejunum; relatively few tumors develop in the central bowel, and only in the lower ileum does the expected number of tumors appear. Available epidemiologic data show a correlation between small intestine cancer and lower, but not upper, gastrointestinal cancer. The incidence of small intestine cancer is positively correlated with protein and fat consumption. (9 Refs)

11. STEROID NUCLEAR DEHYDROGENATION AND COLON CANCER.

Hill MJ
Central Publ. Health Lab., London, England
Am J Clin Nutr; 27(12):1475-1480 1974

A hypothesis on the etiology of colon cancer is presented which postulates that the carcinogen is formed in situ in the colon by the gut bacterial flora from some benign substrate derived from the diet or from some gut secretion produced in response to the diet. According to this hypothesis Clostridium paraputrificum are able to produce a carcinogen or cocarcinogen from bile acids; the concentrations of bile acids in the gut and perhaps also the number of clostridia/gm gut contents is dependent on the nature of the diet. People who have a high concentration of bile acids and large numbers of Clostridium p in the colon are at specially high risk of colon cancer. Evidence in favor of this hypothesis includes the fact that the feces of people in high-incidence countries contain both a higher concentration of bile acids and larger numbers of Clostridium p than the feces of people living in the low-incidence countries, as shown in a previous study of nine normal populations in eight countries. In addition, when the feces from a number of patients with newly diagnosed colon

cancer were analyzed and compared with those from people with diseases other than colon cancer, a high proportion of the colon cancer patients were seen to be in the postulated high-risk group while only a small proportion of the controls fit the high-risk criteria. If this hypothesis is true it implies that colon cancer can be prevented by modifying the diet.

In a study of dietary fat, it was found that a fourfold reduction of fat intake resulted in a three-to fourfold reduction in fecal bile acid concentration with no change in fecal bulk. The effect of fiber on the fecal bile acid concentration depends on the type of fiber used; bran or bulking agents, such as lactulose, mannitol, or sorbitol are useful in reducing fecal bile acid concentration. There is no data on the effect of diet on the numbers of Clostridia p carried by normal adults but indirect evidence indicates that an acid environment in the gut is not conducive to the proliferation of Clostridia p. If this is the case, lactulose in sufficient amounts to reduce the fecal pH to 5 should markedly reduce the numbers of Clostridia p in the gut. Redox systems and transit rate are also considered as factors that might affect the interaction between clostridia and bile acids. It is suggested that transit rate is not unlikely to be of importance in the etiology of colon cancer but that redox systems are of great importance.

12. THE EPIDEMIOLOGY OF CANCER OF THE LARGE BOWEL.

Wynder EL, Reddy BS
American Health Fdn., New York, N.Y.
Am J Dig Dis; 19(10):937-946 1974

The geographic distribution of cancer of the colon, particularly its low incidence in Japan, its increase among Japanese immigrants to the United States, and the high rate of this disease among North Americans and most Western Europeans, indicated that environmental factors were of etiological significance in the development of this disease. Studies in metabolic epidemiology showed a correlation between dietary fat intake and the composition of intestinal microflora, and between the fecal bile acids and cholesterol metabolites. A significant association was established between the level of fecal anaerobic bacteria, bacterial beta-glucuronidase activity, bile acid and cholesterol metabolites, and the risk of colon cancer among different populations. In the rat model, lithocholic acid and deoxycholic acid, present in high concentration in the stool of man, acted as tumor promotors to an established large-bowel carcinogen.

13. METABOLIC EPIDEMIOLOGY OF COLORECTAL CANCER.

Wynder EL, Reddy BS
Am. Health Found., New York, N. Y.
Cancer; 34(3):801-806 1974

On the basis of the geographical distribution of colon cancer and data dealing with migrant populations, it is proposed that the etiology of this cancer is related to dietary factors, particularly animal fats and proteins. Diet, intestinal components of endogenous origin, and intestinal microflora are compared. The unanswered question is what diet-dependent compounds, modified by intestinal microflora in the lumen of the gut, account for development of cancers of the colon. Quantitative aspects of bile acids and natural sterols in the feces of various groups who ate different foods were investigated. The microbial beta-glucuronidase activity in the feces was studied to assess degree of microbial capacity for enzymic hydrolysis of complex conjugates in the large bowel. Also, the ability of pure strains of intestinal microflora to metabolize bile acids and neutral sterols in various products was determined. Data indicated that daily fecal excretion of cholesterol metabolites coprostanol and coprostanone was significantly higher (p less than 0.01) in Americans on a mixed Western diet than any other group; a significant increase in the excretion of total bile acids deoxycholic acid, and lithocholic acid was found in this group. Data on beta-glucuronidase indicate a higher activity in the microflora of persons on this type of high animal protein and fat diet. This finding suggests the possibility of establishing a specific indicator in order to identify individuals at high-risk for large bowel cancer.

14. EPIDEMIOLOGY OF COLORECTAL CANCER.

MacLennan R
Centre International de Recherche sur le Cancer, 150, cours Albert- Thomas, 69008 Lyon, France
Bull Cancer (Paris); 62(4):411-418 1975

Recent epidemiological studies, reviewed here, show that industrialization by itself is not a factor in colorectal cancer. Geographical variations and changes in migrants indicate that dietary factors may have an important effect. High dietary animal fat is believed to stimulate increased biliary secretions and thus provide a substrate for bacterial conversion to carcinogens and cocarcinogens. The association of beef consumption with colorectal cancer may be due to the fat content of beef relative to other meats. Another finding was that, internationally, the consumption of beer is linked more often to cancer of the rectum that to cancer of the colon. The hypothesis that a deficiency in dietary fiber is involved in colorectal cancer has little supportive evidence.

15. ROLE OF BILE METABOLITES IN COLON CARCINOGENESIS.

Reddy BS
Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, Ny 10595
Cancer Suppl; 36():2401-2406 1975

Epidemiological data indicate that colon cancer incidence is associated mainly with high dietary fat intake. Studies in metabolic epidemiology have shown a strong association between dietary fat intake, level of fecal bacteria, fecal acid, and neutral sterols, and the risk of colon cancer among different populations. Current concepts visualize that colonic bile acids and cholesterol metabolites play a modifying role in large bowel carcinogenesis, and that these compounds are derived from dietary factors, directly or indirectly, and subsequently are modified by the intestinal bacteria. In animal models, lithocholic acid and deoxycholic acid, which are present in high concentration in the large bowel of man, acted as promoters of colon carcinogenesis. The carcinogenic effect of azoxymethane in rates was enhanced by the increase of bile salts inthe colon induced by surgical means. Animals fed a high fat diet were more susceptible to colon tumor induction by dimethylhydrazine compared with rats fed a normal fat diet. Our data also demonstrate that the intestinal microflora played a modifying role in accelerating colon tumor production by dimethylhydrazine .

16. THE ETIOLOGY OF COLON CANCER.

Hill MJ
Central Public Health Lab., London, England
CRC Crit Rev Toxicol; 4(1):31-82 1975

Studies of the incidence of colon cancer in populations living in various parts of the world, taken in conjunction with studies of migrant populations, indicate that genetic factors do not play a major part in the etiology of colon cancer. The factors of overwhelming importance are environmental, especially diet (meat and dietary fat). Associated diseases (e.g., atherosclerotic heart disease) and associated cancers (such as prostate, breast, and corpus uteri) indicate a role for steroids in the etiology. The most likely carcinogen or cocarcinogen is an endogenous steroid, in particular the bile acids. Two bile acids, deoxycholic acid and lithocholic acid, have been shown

to be cocarcinogenic in the large bowel. There are two major theories put forward to explain the etiology of colon cancer. Both involve the gut bacteria and both postulate that a carcinogen or cocarcinogen is produced by bacteria from bile acids. The fiber theory attempts to relate the incidence of the disease to the amount of dietary fiber by suggesting that the transit time of material through the gut is of paramount importance. The fat theory suggests that the concentration of bile acids in the large intestine is the most important factor. The weight of evidence to date is strongly in favor of the fat theory.

17. EPIDEMIOLOGY OF CANCER OF THE COLON, DIVERTICULOSIS AND ULCERATIVE COLITIS.

Berndt H

Zentralinstitut fur Krebsforschung, Akademie der Wissenschaften der DDR, DDR-1115 Berlin-Buch, Lindenberger Weg 80, East Germany

Zentralbl Chir; 101(7):402-404 1976

The geographical morbidity and mortality of colon carcinoma, diverticulosis, and ulcerative colitis are surveyed. The higher incidence of colon carcinoma in industrial and urban regions, the global increase in morbidity and mortality, and the higher vulnerability of upper socioeconomic classes are cited. There is a strong epidemiological correlation between colon and mammary carcinoma and between colon and rectal carcinoma mortality that is thought to implicate exogenous, including nutritional, factors. A causal hypothesis is preferred: a high consumption of fat elicits elevations in bile salts, which can be degraded to polycyclic aromatic hydrocarbons by a nonpathogenic intestinal flora. Since there is less intestinal motility in high fat diets, the contact between hydrocarbon and intestinal mucosa is longer and the risk of carcinogenesis greater than in lower fat diets. Diverticulosis is also a disease of industrial countries, with a geographical distribution similar to those of colon carcinoma and coronary artery disease. The highest incidence is in Britain and is attributed to a low fiber diet, incomplete filling of the lumen, and reduced intestinal motility. This elicits increased pressure and contractions and terminates in pulsion diverticula, with oncogenic implications. Ulcerative colitis is also associated with higher standards of living in more industrial societies and among the socioeconomically advantaged. Its relation to intestinal carcinoma remains unexplored.

18. DIET AND CANCER OF THE COLON.

Rowland IR

No Affiliation Given

Food Cosmet Toxicol; 14(3):209-212 1976

In northwest Europe and the United States cancer of the large bowel is responsible for more deaths than any other type except lung cancer. The incidence of colon and breast cancer are very closely correlated and appear to have a common etiology. Positive correlations between cancer of the colon and cancer of the kidney, pancreas, and prostate have been found. All epidemiological studies have provided strong indications of the involvement of environmental factors in cancer of the colon. Additional supportive data have been gained for this theory from studies on immigrant populations moving from low to high risk areas. Mortality in these groups has risen to the level of the surrounding population. The incidence of cancer of the colon appears to reflect the degree of westernization of the diet. The causative agent is still a moot point, but there is good evidence to implicate high dietary concentrations of fat and animal protein. Lack of dietary fiber also appears to be involved, probably because it decreases fecal bulk and thus increases the concentration of carcinogens in the gut.

19. HIGH-FIBRE, LOW-SATURATED-FAT DIET AND THE AETIOLOGY OF COLO-RECTAL CARCINOMATA IN A LOW-RISK POPULATION.

Zaldivar R, Wetterstrand WH

Epidemiological Research Unit, Regional Hospital, National Health Service, Antofagasta, Chile

Z Krebsforsch Klin Onkol; 87(1):41-45 1976

The Chilean population exhibits a very low risk of colo-rectal cancer. The farm workers have a high-fibre, low-saturated-fat diet and also an extremely low age-adjusted death rate for colonic and rectal cancer, in each sex. A highly significant positive correlation between age-adjusted death rates from arteriosclerotic heart disease in males and colonic and rectal cancer death rates suggests that high levels of saturated fats and/or cholesterol in the diet may be incriminated for high death rates from large bowel cancer. It is concluded that high plant fibre content and low levels of saturated fats and/or cholesterol in the diet may be important factors influencing the very low age-adjusted death rates from colo-rectal carcinoma in Chilean farm workers. (Author Abstract)

20. COLONIC CANCER - HYPOTHESES OF CAUSATION, DIETARY PROPHYLAXIS, AND FUTURE RESEARCH.

Walker AR, Burkitt DP

Human Biochemistry, Res. Unit, South African Inst. for Medical Res., Hospital Hill, P.O. Box 1038, 2000 Johannesburg, South Africa.

Am J Dig Dis ; 21(10):910-917 1976

In western populations colonic cancer was uncommon in the past, but now accounts for about 3% of all deaths. The cause almost certainly lies with dietary changes. Probably, alterations within the bowel from interaction between metabolites and microbacteria promote carcinogenesis. Changes in intakes of protein, fat, sugar, refined cereal products, and crude fiber have been advanced as predisposing or causative factors. Evidence suggests that 1) fall in fiber intake and 2) rise in fat intake increase fecal concentrations of bile acids and sterols (possible precursors of carcinogens). If rigorous dietary changes are implemented, an early fall in colonic cancer incidence would be highly improbable due to the long-term character of the disease. Future research must include characterization of the diet, metabolism, and disease pattern of segments of western populations who have low colonic cancer mortality rates, along with the effects of various intakes of different food components on the biochemistry and microbiology of the feces. (71 refs)

21. COLON CANCER AND DIET, WITH SPECIAL REFERENCE TO INTAKES OF FAT AND FIBER.

Walker AR

Hum Biochem Res Unit, So African Inst Med Res, PO Box 1038, Johannesburg 2000, So Africa

Am J Clin Nutr; 29(12):1417-1426 1976

Colon cancer, rare in the past, and in developing populations, currently accounts for 2 to 4% of all deaths in Western populations. Evidence suggests the primary cause to be changes in diet, which affect the bowel milieu interieur. It is possible that in sophisticated populations, the higher concentrations of fecal bile acids and sterols, and longer transit time, favor the production of potentially carcinogenic metabolites. Of secular changes in diet, evidence suggests that the following may have etiological importance: 1) the fall in intake of fiber-containing foods with its effects on bowel physiology, and 2) the decreased fiber but increased fat intakes, in their respective capacities to raise concentrations of fecal bile acids, sterols, and other noxious substances. For possible prophylaxis against colon cancer, recommendations

for a lower fat intake, or a higher intake of fiber-containing foods (apart from fiber ingestion from bran) are extremely unlikely to be adopted. For future research, Western populations with considerably lower than average mortality rates, eg, Seventh Day Adventists, Mormons, the rural Finnish population, as well as developing populations, demand intensive study. Also requiring elucidation are the respective roles of diet and of genetic constitution on concentrations of fecal bile acids, etc, and on transit time, in prone and nonprone populations. (Author Abstract)

22. COLORECTAL CANCER AND DIET IN BLACKS (MEETING ABSTRACT).

Dales LG, Friedman GD, Ury HK, Williams SR, Grossman S

Kaiser Foundation Res. Inst., Oakland, CA 94611

Am J Epidemiol; 106(3):230 1977

In this case-control study, 105 San Francisco Bay Area blacks with colorectal cancer, plus three age-, race-, sex- and residence-matched controls for each case, were interviewed about past dietary habits and other traits. Two of the controls for each case were patients with other diseases from the same hospital, while the third was an outpatient taking a Multiphasic Health Checkup at a Kaiser-Permanente medical clinic. Dietary differences between the cases and controls were generally minimal. However, when analysis was limited to colon/rectosigmoid junction cancer cases and their controls, small and generally non-statistically significant, but suggestive elevations in cancer risk were associated with increased consumption of foods high in saturated fat (particularly pork), while increased consumption of foods high in fiber tended to be associated with a lower cancer risk. These differences in risk were found for both the case-hospital control and case-Kaiser Multiphasic Checkup control comparisons, and they tended to show consistent dose-response gradients. Beef intake was not associated with increased cancer risk. Among women, nulliparity was associated with about a three-fold increase in colorectal cancer risk. Disparity in socioeconomic status did not explain this difference. (Author abstract) (no Refs)

23. TIME TRENDS OF INTESTINAL AND DIFFUSE TYPES OF GASTRIC CANCER IN NORWAY.

Asvall J

Int J Cancer; 8:114-157 1971

Time trends for the 2 main histologic types of gastric cancer were investigated in Norway; tissue samples of gastric cancer were diagnosed as 'intestinal' (i.e, well-differentiated adenocarcinoma), 'diffuse' (i.e, undifferentiated adenocarcinoma), or 'other'. Samples of these types of gastric cancer were drawn from the periods 1940-1944 (I), 1952-1953 (II) and 1960-1964 (III). In period I the intestinal type of gastric cancer was most frequent, accounting for 51.3% of gastric cancer accounted for 39.7% of gastric cancer cases in this period. No difference in this distribution was found between I and II. However, between II and III there was a marked change in the relative frequency of the intestinal and diffuse types, with the former decreasing to make up 35.6% of all gastric cancer cases and the latter increasing to make up 54.2% of all cases. In both sexes the intestinal type was relatively more frequent in the younger age groups. The decline in the intestinal type observed from II to III was greater for females than for males, and it was more pronounced in the under-50-yr-old age group. The gastric cancer death rates in Norway were also examined; it was found that, for both sexes, mortality from gastric cancer fell from the early 1930's to the middle 1960's but that this decline stopped temporarily during the latter half of the 1940's. The general decline in gastric cancer mortality and its interruption in the latter part of the 1940's may be related to dietary factors, specifically to an increase in cereal intake and/or a decrease in the intake of fats, especially milk fats. Dietary changes in Norway brought about by the Second World War may have halted the decline in gastric cancer mortality in period I. Dietary factors influencing the gastric cancer death rate were thought primarily to affect the intestinal type of gastric cancer.

24. RELATIONSHIP BETWEEN CANCER OF THE DIGESTIVE TRACT AND NUTRIENT INTAKE.

Gregor O, Toman R, Prusova F

Charles U., Prague, Czechoslovakia

Rev Med (Paris); 10(13):741-752 1969

Analysis of stomach and intestinal cancer mortality rates from 28 nations (males; 1962-1963) showed a significant positive correlation between intestinal cancer mortality and av dietary levels of total calories (TC) and animal proteins (AP) in 1947-1948 and 1962-1963. Stomach cancer mortality rates showed a significant inverse correlation with respect to dietary TC and AP levels in 1947-1948 only. A significant inverse correlation between stomach and intestinal cancer mortality rates (coefficient -0.85) was also noted. The stomach cancer mortality rate in Czechoslovakia was about 2.9-fold higher than in the U.S, whereas the intestinal cancer mortality rate was nearly 1.9-fold higher in the U.S than in Czechoslovakia. Compared to the av. U.S diet, the av. Czechoslovakian diet has a slightly lower TC content (about 5% below the U.S level), a much higher total carbohydrate level, and much lower levels of AP, fats, and vitamins A, B2 and C (approx. 63%, 70%, 73%, 55% and 75% of the av. U.S levels, resp). It is suggested that the wide difference in stomach and intestinal cancer mortality rates between these 2 nations may be related to the different av. AP levels in the diets. A relationship between these 2 tumors and dietary carbohydrate, fat and vitamin levels was suspected but could not be proved.

B. Dietary Fat and/or Obesity and Breast Cancer

25. OVERVIEW - NUTRITION AND BREAST CANCER.

Wynder EL, Chan P, Cohen L, Hill P

Div. Epidemiology, Naylor Dana Inst. Disease Prevention, Valhalla, NY

Breast; 2(2):11-15 1976

Environmental influences are important in the epidemiology of breast cancer. Women with a high fat diet, as in the Western hemisphere, have a much higher incidence of breast cancer. Epidemiological studies suggest that the etiology of postmenopausal and premenopausal breast cancer differs. Extensive experiments in rats suggest a key role for prolactin, in conjunction with estrogen, in mammary tumor development. These studies indicate that high levels of prolactin stimulate the growth of mammary tumors. Studies in humans are consistent with a hypothesis that the prolactin:estrogen ratio is important in the etiology of breast cancer. Postmenopausal women, who have low levels of estrogen and high levels of prolactin, have more tumors than premenopausal women. However, postmenopausal women on estrogen therapy have fewer tumors, and the onset of the tumors is delayed. The authors are investigating the effects of the prolactin:estrogen ratio on the adenylcyclase system. This system is known to respond to a variety of regulatory hormones by increasing or decreasing the intracellular levels of cyclic AMP, a potent molecule regulating proliferation and differentiation. The authors speculate that the high fat diet, which induces high levels of prolactin, may push the prolactin:estrogen ratio past some threshold point, with the result that growth of a preneoplastic lesion may be enhanced. (41 refs)

26. NUTRITION AND THE ETIOLOGY AND PREVENTION OF BREAST CANCER.

Wynder EL, MacCornack F, Hill P, Cohen LA, Chan PC, Weisburger JH

American Health Foundation, Naylor Dana Inst. Disease Prevention, Valhalla, NY 10595

Cancer Detect Prevent; 1(2):293-310 1976

Evidence from epidemiological and animal studies that relates the consumption of dietary fat to an increased risk of breast cancer, particularly its postmenopausal form, is reviewed. A high-fat diet uniformly increases the incidence of both spontaneous and chemically induced breast cancer in animal model systems. US white women consume about 130-150 g/day of dietary fat, compared to an intake of about 40 g/day for Japanese women. The incidence of breast cancer in these two groups is 22/100,000 and 4/100,000, respectively. However, migrant Japanese, especially those of the second generation, demonstrate an increased incidence. High dietary fat may influence endocrine balance, as elevated prolactin levels are associated with high breast cancer incidence in animal models and in humans. Puberty may be a particularly susceptible period with regard to breast cancer induction by dietary fat. (74 Refs)

27. A STUDY OF DIET AND BREAST CANCER.

Miller AB, Matthews VL, Choi NW, Munan L

Natl. Cancer Inst. Canada, Toronto, Ontario, Canada M5C 1Y2

Am J Epidemiol; 100(6):508 1974

A case-control study is being conducted to investigate the possible association of diet and breast cancer. The hypothesis is based on known population correlates with high fat intake and breast cancer, animal experimental work and the recent demonstration that estrogens may be produced by intestinal bacteria. The assumption is made that recent dietary experience reflects lifetime diet and data on diet is being obtained using a detailed dietary questionnaire, a 24-hr diet recall, and a 4-day diet-diary. Data is also obtained on other epidemiologic variables known to be associated with breast cancer and the analysis will investigate the interaction between these variables and the hypothesized dietary associations. The field work is well under way and is expected to be completed in November 1974.

28. ROLE OF NUTRITION IN THE ETIOLOGY OF BREAST CANCER.

Miller AB

NCIC Epidemiology Unit, Univ. Toronto, 121 St. Joseph St., Toronto M5S 2R9, Ontario, Canada

Cancer; 39(6,Suppl):2704-2708 1977

International differences in breast cancer morbidity and mortality and studies on migrating populations point to the overriding importance of environmental factors in the etiology of breast cancer. Factors directly or indirectly associated with ovarian activity do not appear to explain international differences. Population correlation studies have indicated that much of the difference appears to be explicable on the basis of nutritional factors, particularly, high total fat intake. Animal experimental studies confirm the importance of high fat diet, possibly mediated through prolactin. Other indirect support for the nutritional hypothesis is supplied by changing incidence rates in Iceland, possibly correlated with changing nutritional practices and the association of breast cancer with wt and possibly also with height. The association with height (which would suggest nutritional effects mediated through childhood diet) has not been supported by a study in Canada. Direct investigation of the association between nutrition and breast cancer is difficult because of problems in dietary methodology. Nevertheless, the results of a Canadian case-control study provide support for the importance of high fat intake. Further studies of this question are undoubtedly required, however, before specific recommendations on dietary modification can be made. (Author abstract) (20 Refs)

29. SELENIUM AS A PROTECTIVE AGAINST BREAST CANCER IN NONWESTERN DIETS (MEETING ABSTRACT).

Wilson CS, Petrakis NL

Univ of California, San Francisco, Ca 94143

Fed Proc; 35(3):578 1976

Foods that correlate negatively with incidence and mortality rates for breast cancer present a pattern similar to that of diets of nonwestern people-grains, pulses, fish and fruits. Calculated nutrients in diets of populations of Japan, India and Singapore, where breast cancer incidence is low, differed particularly from the average US diet in content of polyunsaturated fatty acids (PUFA) and selenium. PUFA in these Asian diets range from 7.0-11.7 gm. Published figures for the US are 10-30 gm. The amount of selenium is calculated to be 2 to 4 times higher in Asian than in US diets, chiefly because of greater consumption of grains by Asian people. Selenium has been shown to prevent peroxidative damage from PUFA in tissues of other species through its role as a component of glutathione peroxidase. This enzyme is present in human breast tissue. Ingested lipids are known to reach breast tissue long before they appear in other tissues. Since diets of nonwestern populations in other regions also include good sources of selenium, it is suggested that such diets contribute protection against breast cancer not only through a low PUFA content, but also through the amount of selenium they contain. (Author Abstract)

30. THE EPIDEMIOLOGY OF BREAST CANCER. (PP. 1-20)

Levin ML, Thomas DB

Dept. Epidemiology, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD

Current Trends in the Management of Breast Cancer. Baker RR, ed. Baltimore, Johns Hopkins Univ. Press, 1977.

Risk factors associated with breast cancer are discussed. The high incidence of female breast cancer in the Western world is probably caused by environmental rather than ethnic factors, because migrants from low- to high-risk countries develop breast cancer at intermediate rates. The incidence of breast cancer rises steeply to age 50, flattens out for the next 5 yr, and then increases again. The change in the rate at the age of menopause suggests that endogenous hormones are of etiologic importance. Women whose age at first birth was greater than or equal to 35 yr have a greater than 50% higher risk than the general population. The risk is lower in women with late menarche and early menopause, either artificial or natural. Urinary excretion of low levels of androgen metabolites and excretion of the inactive form of these substances are associated with an increased risk. Urinary estriol excretion is associated with a decreased risk. These excretion patterns indicate endocrinologic abnormalities at the breast tissue level that may play a role in the genesis of breast cancer. Obesity and dietary fat, also positively correlated with an increased risk, may be related to breast cancer development because of associated changes in endogenous hormones. A relationship between exogenous estrogens and breast cancer has not been proved. There is evidence that an oncogenic RNA virus or high doses of ionizing radiation may be involved in the genesis of breast cancer. A relationship is suspected between fibrocystic breast disease and increased risk, as well as between treatment of hypertension with reserpine and increased risk. Oophorectomy before age 35 appears to have a protective effect. (80 Refs)

31. NURTURE AND NATURE IN CANCER OF THE BREAST AND THE ENDOMETRIUM. (PP. 121-130)

De Waard F

Host Environment Interactions in the Etiology of Cancer in Man Proceedings of a meeting held at Primosten, Yugoslavia, 27 August-2 September 1972 ; International Agency for Res. on Cancer (Lyon, France): Natl. Insts. Health (USA): 1973

Correlations computed from data on cancer incidence in five continents among women (notably, breast cancer) were tabulated to see if there are any environmental effects on endocrine regulation. There were no correlations between cervical cancer and any of the other neoplasms, whereas colon cancer was highly correlated with breast and endometrial cancer and slightly less so with ovarian cancer. Climate or geographic latitude slightly less so with ovarian cancer. Climate or geographic latitude has no effect; it is suggested that the low incidence of these last four cancers in Japanese women may be due to nutrition. The age-specific breast cancer incidence curves of most populations in Asia, Africa, and the Middle East rose up to age 50, followed by a leveling-off or a decline; in Western countries the leveling-off phenomenon was followed by a steep rise after age 55. In the U.S, however, this phenomenon was not usually seen. The rising incidence of breast cancer does not seem to follow a simple relationship to age. An increase in potency of a carcinogenic stimulus may, with time, overcome the postmenopausal leveling-off trend seen most clearly in populations following a non-Western way of life.

A hypothesis is presented to account for geographical differences in breast cancer incidence: (a) there may be two etiologically different types of breast cancer (with different age distributions that overlap in the of breast cancer (with different age distributions that overlap in the 40- to 50-yr range). (b) The type that usually occurs in the premenopausal 40- to 50-yr range). (b) The type that usually occurs in the premenopausal age group may be related to a hormonal abnormality involving ovarian function. (c) The second type, which occurs mostly in the postmenopausal group, may be etiologically related to nutritional habits prevalent in the Western world, especially to obesity. Results from a study of the relationship between urinary sediment smears in postmenopausal women and breast cancer are summarized; the smears classified as intermediate (rather than estrogenic or atrophic) are associated with the highest risk; overweight is also a risk factor. It is suggested that lean women in Western countries might have an incidence curve similar to that of Japanese women. It is recommended that future studies include data on the weight and height of all new breast cancer patients to determine how many of the geographical differences in breast cancer incidence can be explained by measurable population characteristics related to overweight.

32. CURRENT VIEWS ON BREAST CANCER (I).

Estape J

No affiliation given

Med Clin; 63(7):366-370 1974

The current knowledge of the epidemiology of breast cancer is reviewed. Incidence rates have increased and mortality rates have decreased in the last 30-40 yr. Some controversial statistics reported in the literature are mentioned. The mortality versus age relationship indicated that breast cancer is the main cause of death in women 30-40 yr of age. Previous cancer in one breast or a familial history of cancer are the highest risk factors. High fat diet, obesity, and disturbances in carbohydrate metabolism are mentioned among the metabolic factors. Genetic studies indicate a higher incidence of breast cancer in patients with antigenic determinant A in the ABO blood group system. A possible viral etiology of breast cancer in humans is still under investigation without conclusive results. New viral particles, defined as MS-1, MS-2 and MS-3, detected in humans have characteristics similar to those of the B particles in mammary carcinoma virus of the rat. Women from the Parsi tribe of India, with high incidence of breast cancer, had more viral particles in their milk than American women with or without familial risk of breask cancer. Viral particles similar to those found in rats with breast cancer were discovered in an 8-yr-old Maccacus Rhesus with spontaneous breast tumor. Cellular type immunological reactions are sometimes observed in women with breast cancer, more frequently in Stage I patients than in Stage 2 patients; these responses are similar to those detected in experimental breast tumors. The hormone-dependent factors, mainly ovarian estrogens, are held responsible for the development of breast cancer in one-third of the cases. No conclusive evidence exists that contraceptive compounds are carcinogenic.

33. EPIDEMIOLOGICAL CHARACTERISTICS OF BREAST CANCER IN MIDDLE AND LATE AGE.

Hems G

U. Med. Building, Foresterhill, Aberdeen, Scotland

Br J Cancer; 24(2):226-234 1970

Data for different countries were examined for associations between breast cancer rates at 40-44 yr and at 65-69 yr with diet, parity, birth rate and blood group, with the re lt that a positive correlation between breast cancer and sugar and fat intakes was found. The correlation explained three-quarters of the variation in the 'late rate' (65-69 yrs), for 22 countries, but only half of the variation in the 'early rate' (40-44 yrs). The late rate was, further, positively correlated with estimates of the percentage of nulliparous women (9 populations) and, together with terms for sugar and fat intakes, the multiple regression explained 90% of the variation. Early registration rates (13 populations) were positively correlated with blood group A which appeared, from the multiple regression equation, to contribute more than twice the amount to the early rate than did sugar and fat intakes. The contribution of blood group A to the late rate appeared to be only one-third of that for sugar and fat intakes. The results may indicate that the late breast cancer rate was influenced by environmental factors of food and diet and by factors associated with childbirth, whereas the crucial factor influencing the early rate was a constitutional factor, blood group A.

34. GUT BACTERIA AND AETIOLOGY OF CANCER OF THE BREAST.

Hill MJ, Goddard P, Williams RE

St. Mary's Hosp. Med. Sch., London, England

Lancet; 2(7722):472-473 1971

Geographical variations in the incidence of mammary carcinoma seem to be correlated with variations in the fat content of diets. A hypothesis relating diet, intestinal bacteria and mammary carcinoma is presented. The hypothesis requires that intestinal bacteria be able to produce from steroids associated with a high-fat diet a carcinogen that might act on mammary tissue or an estrogen that might stimulate tumor growth. The production by intestinal bacteria of estradiol, estrogen, and 17-methoxy-estradiol from androstenedione and from cholestenone and 3-oxo-chol-4en-24oic acid has been demonstrated. Cholestenone is present in feces and is a bacterial metabolite of cholesterol. Intestinal bacteria have also produced 3-oxo-chol-4en-24oic acid from fecal bile-acids. The amount of steroidal estrogen produced by intestinal flora varies greatly from person to person but on average is believed much higher in people living on a normal Western diet than in those living on the low-fat diets common in Africa, Asia and South America. Since people living on a

high-fat diet excrete on the average an estimated 600 mg per day of acid and neutral steroids, intestinal bacteria need aromatize only a very small proportion of this potential substrate to make a highly significant contribution to mammary carcinoma development.

35. STEROID HORMONES AND HUMAN BREAST CANCER. AN HYPOTHESIS.

Adams JB

Sch. Biochemistry, Univ. New South Wales, P.O. Box 1, Kensington, N.S.W. 2033, Australia

Cancer; 40(1):325-333 1977

The likely occurrence of two distinct types of human breast cancer is discussed. In the development of the "Western-environmental" or "adrenal" type, it is proposed that dehydroepiandrosterone sulfate (DHEAS), secreted by the adrenal, may be implicated. This steroid is metabolized by mammary tumors to active androgens and estrogens. That these metabolic pathways are very similar to that in skin is emphasized and this is possibly explained by evolution of the mammary gland from primitive sweat glands. Formation of DHEAS from DHEA in mammary tumors, claimed to be correlated with an individual subject's prognosis and response to hormone ablation, is discussed in the light of a possible regulatory role of the sulfhotransferase. It is proposed furthermore that a specific control of DHEAS secretion in the adrenal may exit at the level of the sulfhurylation step. Nutritional factors are also possible implicated here and there are discussed in light of: a possible higher secretion rate of DHEAS in obese subjects; and the low breast cancer incidence in the Japanese and the accompanying low blood DHEAS levels. (Author abstract) (53 Refs)

36. GEOGRAPHIC, REPRODUCTIVE AND SOCIOBIOLOGICAL FACTORS IN BREAST CANCER. (PP. 25-53)

Thomas DB, Lillenfeld AM

Risk Factors in Breast Cancer. Edited by BA Stoll Chicago William Heinemann Medical Books, New Aspects of Breast Cancer, vol. 2, 1976.

Geographic, reproductive, and sociobiological factors are surveyed, along with possible interrelationships between these factors and their mechanisms of action. Death rates due to breast cancer vary markedly; they tend to be high in the developed countries with populations of predominantly European descent and low in less-developed countries, especially those with non-Caucasian populations. In the past three decades the mortality rates in most predominantly European populations, if high, have remained stable, and if low, have increased. Environmental factors appear to have a greater effect on postmenopausal women than premenopausal women. Evidence of environmental factors has been obtained through immigrant studies, which show that migrants tend to develop breast cancer at a rate more comparable to the country of adoption than the country of origin. Single women are at a higher risk than married women, and married women who have never been pregnant are at a higher risk than those with children. A striking relationship between risk of breast cancer and age at either natural or artificial menopause has been noted. No associations with other menstrual factors have been found consistently. The disease occurs more frequently in women of higher socioeconomic status and in women who are obese or who have rich fat diets. Reserpine and ionizing radiation have also been implicated. In male breast cancer, many of the same risk factors have been observed.

C. Obesity and Endometrial Cancer

37. ASSOCIATION BETWEEN TEEN-AGE OBESITY AND CANCER IN 56,111 WOMEN: ALL CANCERS AND ENDOMETRIAL CARCINOMA.

Blitzer PH, Blitzer EC, Rimm AA

Medical Coll. Wisconsin, 1725 West Wisconsin Ave., Milwaukee, WI 53233

Prev Med; 5(1):20-31 1976

Historical data from 56,111 women of varying obesities (members of TOPS Club, Inc) were analyzed for association of teenage obesity with prevalence of all cancers and with endometrial carcinoma. This study shows no relationship between obesity level and cancer in general. Women who were of high obesity as teenagers had a relative risk of 1.62 of developing endometrial carcinoma compared to women who were of low obesity as teenagers. The relative risk was 1.75 for those highly obese both currently and as teenagers. Results indicate that teenage obesity may predispose to endometrial carcinoma, confirming reports based on observation of hospital-drawn endometrial carcinoma populations, and supporting the theory that obesity induces estrogens predisposing to endometrial carcinoma. Limitations of TOPS women as a study population include: absence of underweight women to indicate the effect of thinness; selection of women concerned about their obesity; and exclusion of women with a history of cancer who, reacting nihilistically to the diagnosis, would not join TOPS.

38. THE ETIOLOGY OF UTERINE CANCER.

Schindler AE, Glaeser F

Univ. Clin. Gynecol., Tubingen, Germany

Geburtshilfe Frauenheilkd; 34(3):186-194 1974

Clinical and hormonal risk factors were statistically evaluated in 142 patients with uterine cancer and in a control group of the same size. The average age at onset was 63.63 yr and the average age at menopause was 50.4 yr; both values are higher than those found in previous studies. Most patients with uterine cancer (23.2%) were between the ages 55 and 59 yr. Diabetes mellitus was found in 38% of the uterine cancer patients and in 15.3% of the controls. Hypertension was found in 57% of the cancer patients and in 32.3% of the controls. Symptoms of severe obesity were more frequent among uterine cancer patients than in the control group. The incidence of the estrogen effect in vaginal smears of the cancer group did not differ appreciably from that in the control group (51% and 47.1%), only 25.8% of the controls showed evidence of endometrial proliferation in comparison to 47.2% of the cancer patients. Thus, the risk of developing uterine carcinoma is highest in subjects with obesity, diabetes mellitus, hypertension and with estrogen effect in the vaginal epithelium or endometrium after menopause.

39. A STRATEGY FOR THE CONTROL OF ENDOMETRIAL CANCER (MEETING ABSTRACT).

Gusberg SB

Dept. Obstet. Gynecol., Mount Sinai Sch. Med., New York, N.Y.

Proc R Soc Med; 68(3):163-168 1975

Geographic differences in the incidence of endometrial cancer suggest that nutritional status is significant, especially as it impinges on the endocrine system. Evidence of hormone sensitivity in endometrial cancer includes the greater risk for women with obesity, infertility, failure of ovulation, dysfunctional bleeding, diabetes, the effect of progesterone on metastatic endometrial cancer, adenocarcinoma of cervix and vagina in adolescent offspring of diethylstilbestrol-treated mothers, development of endometrial carcinoma in young women treated with estrogen for ovarian agenesis, and

induction of precursor with exogeneous estrogens. Adenomatous hyperplasia in young women may be treated by induction of ovulation if infertility is a problem; in others, cycling with progestin will usually effect reversion to normal. Aspiration curettage is an accurate histologic screening measure for all high-risk women at the menopause. In postmenopausal women in whom bleeding occurs spontaneously in the absence of estrogen treatment, a formal diagnostic curettage is indicated since a significant percentage will harbor true cancer. Identification of virulence factors ensures that each patient with endometrial cancer receives adequate treatment for cure while avoiding unnecessary therapeutic penalties. Clinically applicable factors are depth of uterine cavity (size of tumor), histologic differentiation of tumor (capacity for penetration), and involvement of the isthmus and cervix (drainage to pelvic lymphatic channels and nodes). A clinical staging classificatior. based on these discriminants permits the selection of treatment as follows: simple hysterectomy and bilateral salpingo-oophorectomy for Stage I tumors (local 'dependent'), combined treatment with preoperative radium packing for Stage II (direct local spread), combined treatment with radical hysterectomy and pelvic lymphadenectomy for Stage III ('biologic' spread), and individual treatment for Stage IV (widespread 'autonomous' tumor). Possible variations in this general protocol are outlined. (47 ref)

40. HORMONES, BODY BUILD AND ENDOMETRIAL CANCER.

de Waard F

Dept. Epidemiology, Inst. Social Medicine, Univ. Utrecht, The Netherlands

Acta Cytol (Baltimore); 19(5):486-487 1975

Hormones, socioeconomic conditions and obesity are discussed in relation to endometrial cancer. Epidemiological studies have been made of the cytologic phenomenon of postmenopausal estrogenic smears. "Post menopausal estrus" has been found associated with diabetes, hypertension, late menopause, and especially obesity. Its prevalence is suggested to be dependent on nutritional abundance and on Western life styles. The incidence of endometrial cancer in South African Bantu women living in Johannesburg is thought to be the result of improved socio-economic conditions.

41. CANCER RISK AND ESTROGEN USE IN THE MENOPAUSE.

Ryan KJ

Boston Hosp. for Women, Boston, Mass. 02115

N Engl J Med; 293(23):1199-1200 197

Some estrogens are produced from body fat during the menopausal years; the amount produced is proportional to total body weight, paralleling the increased risk of endometrial cancer with obesity. Two studies indicate that the risk of endometrial cancer is increased 5-14-fold by administration of estrogen . The increase in risk caused by obesity is estimated to be 3-9-fold. A protective effect of estrogen against heart disease has been largely discredited. Prior thromboembolic events, migraine headaches, family history of cancer, and/or excessive smoking should be weighed as contraindications to estrogen use.

42. USE OF ESTROGEN PREPARATIONS AFTER MENOPAUSE AND THE RISK OF ENDOMETRIAL CARCINOMA.

de Waard F

No affiliation given

Ned Tijdschr Geneeskd; 120(29):1263-1264 1976

The increase in endometrial carcinoma during the last 20 yr and its possible causes are examined. Obesity and the concomitant continuous production of estrogen in adipose tissue are the main predisposing factors, because of their prevalence in the Western hemisphere. The noncyclic use of estrogen preparations by postmenopausal women increases the risk of endometrial cancer four- to sevenfold. This iatrogenic factor can be reduced by switching to cyclic therapy or to drugs with a lesser influence on the endometrium. (6 Refs)

43. HORMONAL DYNAMICS ASSOCIATED WITH THE MENOPAUSE.

Judd HL

Univ. California, San Diego, Sch. Medicine, La Jolla, CA

Clin Obstet Gynecol; 19(4):775-788 1976

The endocrinology of premenopausal and postmenopausal androgens and estrogens is reviewed in relation to endometrial carcinoma. The levels of circulating androstenedione and testosterone, and the clearance and generation rates for testosterone, are very similar in both pre- and postmenopausal women with or without endometrial cancer (EC). The rate of androstenedione generation was originally found to be similar in postmenopausal women with or without EC. Recent evidence finds a greater androstenedione secretion in postmenopausal women with EC, which elevation is approximately equal to that in the premenopause. The mean circulating levels of estradiol and estrone are similar in postmenopausal women with EC compared to levels in nontumor patients, based on a body weight correlation. The positive correlation of estradiol-estrone levels with obesity confirms the in-vitro finding that fatty tissue aromatizes androgens. It follows that estrogen metabolism is similar in both postmenopausal women with EC and weight-matched controls, and that obesity is a risk factor in EC. Although it is known that high postmenopausal gonadotropin levels result from increased pituitary sensitivity to luteinizing hormone-releasing factor due to low estrogen levels, the relation between gonadotropin and EC has not been clarified. (48 refs)

D. Fat and Cancer of Multiple or Miscellaneous Sites

44. DO POLYUNSATURATED FATS PREDISPOSE TO MALIGNANT MELANOMA?

Goldrick RB, Goodwin RM, Nestel PJ, Davis NC, Poyser A, Quinlivan NL

Dept. Clinical Science, Australian Natl. Univ., P.O. Box 334, Canberra City, A.C.T. 2601, Australia

Med J Aust; 1(26):987-989 1976

A comparison was made of the consumption of polyunsaturated fats (PUF) by 29 patients with malignant melanoma and 31 control patients with benign pigmented nevi. The consumption was estimated retrospectively by analysis of linoleic acid content in biopsied adipose tissue and by questioning the patients about their past dietary practices. It was found that the melanoma patients had not consumed excessive quantities of PUF, providing no evidence that the ingestion of PUF is in any way associated with an increased risk of melanoma. (12 refs)

45. DO POLYUNSATURATED FATS PREDISPOSE TO MALIGNANT MELANOMA? LETTER TO EDITOR.

Mackie BS

187 Macquarie St., Sydney, New South Wales 2000

Med J Aust; 2(21):806 1976

The possible association of polyunsaturated fats with malignant melanoma is assessed. In January, 1972, a patient was seen who had been previously treated over a period of years for simple keratoses, and developed three separate squamous cell carcinomas of the skin within 4 mo. The only significant fact was that he had changed to a polyunsaturated

fat diet 6 mo before the first squamous cell carcinoma appeared. It was suggested that he go back to his previous diet, and he has not had a squamous cell carcinoma since. In the next 2 yr, two more patients were seen with the same story and the same result. In the summer of 1973-1974, five patients with malignant melanoma were observed. These patients required extensive surgery, and they had to cope with the threat of metastases. A dietitian interviewed four of the five patients, and she determined that all of them had substantially reduced their intake of saturated fat and replaced it with polyunsaturates. The fifth patient was under the supervision of a cardiologist, who indicated that the diet was fully polyunsaturated. Patients with primary lesions on sites of most frequent trauma might show less evidence of a dietary factor than other melanoma patients. The sites of most frequent trauma are the head and neck, the hands and feet, the groins, axillae, genitals and buttocks. Lesions with the highest malignant activity would be likely to show the strongest causative influences and perhaps a combination of factors. A series of patients with metastases may well demonstrate more evidence of a dietary factor than those with secondary spread. A significant difference between fat analyses for the cases of traumatic lesions and those metastases would be evidence that dietary lipids are involved. (3 Refs)

46. LYMPHOMAS AND DIETARY FAT (LETTER TO EDITOR).

Palmblad J
Dept. Medicine IV, Sodersjukhuset, and Lab. Clinical Stress Res., Karolinska Inst., S-104 Stockholm 60, Sweden
Lancet; 1(8003):142 1977

The relationship between fat ingestion and lymphoma development is under investigation. Lipid interference with lymphocytic and phagocytic function may be related to defense against carcinogenesis. The granulocyte bactericidal capacity (GBC) was analyzed in a group of 12 obese (mean wt, 131 kg) men, and a control group of men (mean wt, 69 kg). A significant difference was observed (p less than 0.01) in the GBC of the obese group, as measured in the percentage of colony forming units after 90 min of incubation. The lipid effect may be a contributory factor in lymphoma development. (9 refs)

47. CANCERS OF THE PANCREAS AND BILIARY TRACT: EPIDEMIOLOGICAL CONSIDERATIONS.

Fraumeni JF
Natl. Cancer Inst., Bethesda, Md. 20014
Cancer Res; 35(11/Part2):3437-3446 1975

Epidemiological patterns for pancreatic and biliary cancers reveal more differences than similarities. Pancreatic carcinoma is common in western countries, although two Polynesian groups (New Zealand Maoris and native Hawaiians) have the highest rates internationally. In the United States, the disease is rising in frequency, predominating in men and in blacks. The rates are elevated in urban areas. The origin of pancreatic cancer is obscure, but a two-fold increased risk has been documented for cigarette smokers and diabetic patients. Alcohol, occupational agents, and dietary fat have been suspected to be risk factors. The reported incidence of biliary tract cancer is highest in Latin American populations and American Indians. The tumor predominates in women around the world. In the United States, the rates are higher in whites than blacks, and clusters of high-risk counties have been found in the north central region, the southwest, and Appalachia. The distribution of biliary tumors parallels that of cholesterol gallstones (the major risk factor for biliary cancer). Insights into biliary carcinogenesis depend upon clarification of lithogenic influences, such as pregnancy, obesity, and hyperlipoproteinemia, exogenous estrogens, familial tendencies, and ethnic-geographic factors that may reflect dietary habits. Noncalculous risk factors for biliary cancer include ulcerative colitis, clonorchiasis, Gardner's syndrome, and probably certain industrial exposures. Within the biliary tract, tumors of the gallbladder and bile duct show epidemiological distinctions. Bile duct neoplasms predominate in men; they are less often associated with stones and more often with other risk factors. In some respects, bile duct and pancreatic tumors are alike. The male predominance of both tumors, an association between cholecystectomy and pancreatic cancer, and other considerations have prompted the notion that the same biliary carcinogens may affect the bile duct, ampulla of Vater, or (by reflux) the pancreatic duct.

48. STUDIES IN THE EPIDEMIOLOGY OF PROSTATIC CANCER: EXPANDED SAMPLING.

Rotkin ID
Univ. Illinois Coll. Medicine, Chicago, IL 60612
Cancer Treat Rep; 61(2):173-180 1977

As a result of comparison of 111 prostatic cancer patients with matched control patients for selected risk variables, the patients are characterized by three main trends: delayed sexual drive and development, early repression of sexuality, and premature cessation of sexuality. Excessive numbers of patients reported occupational exposure to fertilizers and auto exhaust fumes. Diets of the patients were higher in animal fats. There were no differences between both groups in frequencies of multiple marriages or sex partners or stressful effects from selected events early or late in life. Trends for circumcision and other variables are presented. The data suggest that early differences are hormonally conditioned, they support a provisional endogenous rationale for initiation of prostatic cancer, and they oppose a hypothesis favoring transmissible oncogenic agents. If the results continue to hold up with increased sampling, limitation of sexual activity at any time of life may increase risk. (3 Refs)

49. EPIDEMIOLOGY OF SKIN CANCER IN NEW ZEALAND.

Eastcott DF
48 Cuba Street, Petone, New Zealand
Natl Cancer Inst Monogr; 10:141-151 1963

A retrospective study of skin cancer cases in New Zealand showed incidence rates of 5 per million, (male and female) at age 25; approximately 80 male and 50 female at age 35; 300 and 100 at 55; and 500 and 200, resp, at 65. For males the rate is 5-6 times, and for females, 2-3 times the French rate. Estimated total yearly rates of skin cancers were: malignant melanoma 55; basal-cell carcinoma 1,130; and squamous-cell carcinoma 380. Malignant melanoma, while much higher than in Britain and the USA, was not as high as in Australia. Basal-cell carcinoma was more prevalent in New Zealand than in Britain, and higher than in Australia, the highest frequency was on the head and neck. The prime etiologic agent seemed to be sunlight, especially among fair-skinned persons. The distribution pattern of facial sites concentrated near sebaceous glands, and the overall high incidence in New Zealand, with its high dietary animal fat intake, might be accounted for by the assumption that, where fatty material is concentrated, sunlight acts upon some skin precursor (like that for Vitamin D) to render it carcinogenic. A high frequency of chronic lymphatic leukemia was found among males with basal-cell and squamous-cell carcinoma (6/446, expected incidence, 0.2/446).

50. DIET AND CANCER OF ENDOCRINE TARGET ORGANS.

Cole P, Cramer D

Dept. Epidemiology, Harvard Sch. Public Health, 677 Huntington Ave., Boston, MA 02115

Cancer; 40(1,Suppl):434-437 1977

The role of diet in the etiology of cancer of the breast and endometrium is considered. Geographic variation in rates, effects of migration, consequences of exogenous hormone use, and other epidemiologic factors are reviewed. Cancer of the endometrium is related to diet probably through simple caloric excess. The excess is reflected in obesity and the consequent overproduction of estrone, a natural but carcinogenic human estrogen. Diet may also influence breast cancer risk somewhat through the same mechanism. But this mechanism probably would not explain a large proportion of the disease. It is possible that, in addition, some specific dietary factor, for example, saturated fat, is causally related to breast cancer. Such a relationship would probably be mediated through an endocrine mechanism. (Author abstract) (26 Refs)

51. DIET AND ENDOCRINE-RELATED CANCER.

Hill P, Chan P, Cohen L, Wynder E, Kuno K

Naylor Dana Inst for Disease Prevention, Valhalla, NY 10595

Cancer Suppl; 39(4):1820-1826 1977

In women, dietary modification and life style affect the risk of breast cancer and may alter the hormonal status, while in experimental animals diet can alter the incidence of induced mammary tumors. In this study, a high fat diet increased the incidence of DMBA-induced tumors in rats while this increase in incidence was lowered and the effect of a high fat diet obliterated by an anti-prolactin during CB154. Premenopausal Japanese women had a higher estradiol level than their Caucasian counterpart. In Japanese but not Caucasian breast cancer patients, the estradiol decreased. When nurses were transferred from the Western to a vegetarian diet, the menstrual cycle was shortened, while their prolactin and testosterone decreased. Data indicate that dietary factors influence tumor incidence and hormone profile in rat mammary cancer and the hormonal status in women. (38 Refs) (Author Abstract)

52. THE ASSOCIATION BETWEEN COLORECTAL CANCER AND BREAST CANCER.

Howell MA

Division of Cancer Cause and Prevention, NCI, Bethesda, MD 20014

J Chronic Dis; 29(6):243-261 1976

Evidence for an association between colorectal cancer and breast cancer is reviewed. Consistent with a dietary hypothesis to account for a relationship between the cancer sites, intestinal and breast cancers show a similar pattern in correlations of cancer mortality and incidence rates with per capita food consumption figures. The international data indicate that meat, particularly cattle meat, is the food most closely associated with both colorectal and breast cancer rates. In the one case-control study which has shown dietary factors to be related to colorectal cancer, the specificity of beef as the most suspect food item implied the need for studies of long-chain, saturated fatty acids. A high animal fat and protein diet could also mean elevated levels of dietary tryptophan. Studies of tryptophan metabolism are viewed as suggestive of a biochemical mechanism for the interaction of nutritional and hormonal factors. A hormonal mechanism affected by dietary fat has similarly been postulated and has some experimental support. Possible research in further exploration of an association between colorectal and breast cancers is suggested. (Author Abstract)

53. BRIEF COMMUNICATION: CHARACTERISTICS IN YOUTH INDICATIVE OF ADULT-ONSET HODGKIN'S DISEASE.

Paffenbarger RS, Wing AL, Hyde RT

California State Dept of Health, 2151 Berkeley Way, Berkeley, CA 94704

J Natl Cancer Inst; 58(5):1489-1491 1977

From the college entrance health data of 50,000 male former students, the records of 45 who eventually died of Hodgkin's disease were compared with those of 180 surviving classmates with reference to certain indicator characteristics. Risk ratios of Hodgkin's disease tended to be lower for men who had experienced various common contagious diseases in childhood. This reduced incidence of clinical contagions may signify that: 1) Inadequate early challenge of immune mechanisms left subjects more susceptible to later Hodgkin's disease, whether or not it is of infectious origin; 2) heightened immune mechanisms that led to subclinical attacks of early contagious diseases promoted an autoimmune response that evolved as Hodgkin's disease; or 3) early childhood infections eliminated some subjects who otherwise would have attended college and ultimately developed adult-onset Hodgkin's disease. Also, Hodgkin's disease risk was higher for students who had reported early death of a parent, particularly from cancer. Moreover, the risk tended to be increased among collegians who were obese, heavy cigarette smokers, and coffee drinkers. None of these indicator characteristics was associated with 89 fatal lymphomas of other types that occurred in the same study population. (15 Refs) (Author Abstract)

II. NUTRITIONAL ASPECTS OF HUMAN CANCER INCIDENCE

A. Nutritional Studies Including Fat and General Cancer Incidence

54. STATUS OF RESEARCH ON NUTRITION AND CANCER: CONCLUDING REMARKS.

Wynder EL

Naylor Dana Inst. Disease Prevention, New York, N.Y. 10019

Cancer Res; 35(11Part2):3548-3550 1975

The most promising leads in the etiology of cancer with respect to diet are summarized. It is recommended that all individuals lower their intake of total fat, calories, and cholesterol.

55. NUTRITION AND CANCER.

Wynder EL

Naylor Dana Institute for Disease Prevention,American Health Foundation, New York, New York,10019

Fed Proc; 35():1309-1315 1976

There is increasing epidemiological evidence that nutrition plays a dominant role in the pathogenesis of several types of human cancers. There is considerable epidemiological evidence showing that alcoholism, in part because of associated nutritional deficiencies, significantly increases the risk of smokers for cancer of the alimentary tract. There is also some suggestion that nutritional deficiencies may relate to cancers of the stomach, cervix, and thyroid. Of particular importance, and based on relatively new concepts, are data indicating that overnutrition significantly affects the development of certain cancers, including cancer of the colon and pancreas, kidney, breast, ovary, endometrium, and prostate. Except for cancer of the endometrium, and kidney cancer in women, there is no significant relationship to obesity. Rather, the evidence suggests both epidemiologically

and experimentally that the etiological factors relate to a high intake of fats and possibly other variables associated with high fat intake. While we are investigating the mechanistic nature of the epidemiological and experimental observations, the question that needs to be asked is whether it is not prudent for us to associate ourselves with the recommendations of our colleagues in the cardiovascular disease field who call on both individuals and the food industry to practice a 'Prudent Diet,' i.e, one that is lower in total calories, total fat, saturated fats and cholesterol than is the present American diet. (Author Abstract)

56. NUTRITION AND CANCER.

van der Linde F

Zurcher Krebskrankenregister, Nelkenstr. 15, CH-8006 Zurich, Switzerland

Zentralbl Bakteriol Orig B; 163(1/4):128-152 1976

The problem of a relationship between nutrition and cancer has to be approached from two different points of view: direct effect of carcinogens present in foods or in food additives (direct carcinogenesis) and in vivo synthesis of carcinogens caused by changes in metabolism due to altered dietary habits (indirect carcinogenesis). The effects of nutritional deficiency and nutritional excess must be distinguished for the second mechanism. In man, possible relationships between nutrition and cancer are postulated mainly for tumors of the gastrointestinal tract and for hormone-dependent cancers. Epidemiological evidence points to the major importance of indirect carcinogenesis caused by specific nutritional deficiencies and excesses. As experimental studies in man are difficult to perform, most hypotheses are based on statistical associations; caution is required in drawing inferences on causal relationships.

Cancers of the upper and lower gastrointestinal tract epidemiologically behave in a different way, the former showing a marked decrease in most western countries, the latter a slight increase. The etiology of cancers of the esophagus and stomach has yet to be determined. Migrant studies show a major effect of environmental rather than genetic factors. Substantial differences in dietary habits between countries with high and low incidence of stomach cancer point to the importance of nutrition as an etiological factor; no specific dietary components have been identified so far. Recent hypotheses suggest that dietary factors may relate to cancer of the colon by their effect on bile production and on the bacterial makeup of feces, which in turn might be transforming bile acids into active carcinogens. There is, however, disagreement about the specific dietary component responsible for this model of carcinogenesis. Lower consumption of dietary fiber may result in retarded bowel function and additional time for bacterial proliferation and degradation by bacteria of bile acids. It is also hypothesized that increased bile acid and neutral sterol excretion and microbial modification of these compounds with the high content of animal fat in the western diet may cause this bowel cancer. With hormone-dependent cancers, a correlation has been shown between body wt and height and breast cancer as well as between obesity and cancer of the endometrium. Some dietary aspect may cause a hormone metabolism change responsible for increased cancer risk. (126 Refs)

57. DIET, NUTRITION, AND CANCER.

Alcantara EN, Speckmann EW

Division of Nutrition Research, National Dairy Council, 6300 North River Road, Rosemont, Illinois 60018.

Am J Clin Nutr; 29(9):1035-1047 1976

As the second leading cause of death in the United States, cancer is a major public health problem today. Cancer incidence varies worldwide and tends to change with migration. These epidemiological observations have led to the concept that environmental factors may be important in carcinogenesis. Diet and nutrition are receiving increased attention and the National Cancer Institute, as mandated by the National Cancer Act Amendments of 1974, is playing a major leadership role in expanding research efforts in the areas of environmental carcinogenesis, and nutrition in relation to cancer. The subject of diet, nutrition, and cancer is complex. Different types of cancer are not necessarily affected by dietary components in the same manner. Although the development of certain neoplasms may be repressed by specific dietary deficiencies, other types, particularly those of the liver and upper gastrointestinal tract, are actually augmented or potentiated by such deficiencies.

In extrapolating results from animal experiments to humans, caution must be exercised because of possible differences in species response to the same dietary stimulus and because spontaneous tumors may react differently from experimentally-induced tumors. Diet and nutrition are viewed more appropriately as modifiers, rather than initiators, of tumorigenesis. Caloric intake, type and amount of fat, protein, amino acids, vitamins, minerals, fiber, and other dietary constituents have been studied in regard to their influence on the development of neoplasms. Dietary components may have opposing effects on tumorigenesis, ie, protective and predisposing, and the consequence to the host will depend on the balance between these opposing forces. Studies conducted to date indicate that the modifying effect of diet and nutrition may be exerted through specific effects on 1) intestinal bacteria and substrates for bacterial metabolism, 2) microsomal mixed-function oxidase system, 3) endocrine system, 4) immunological system, 5) availability of metabolites for cell proliferations, and 6) rate of carcinogen transfer and duration of exposure to the carcinogen. More research is needed to elucidate the interaction between diet and each of these factors and to test the validity of the mechanisms proposed to explain such interactions. These studies will lead not only to a better understanding of carcinogenesis itself but also to a new understanding of the influence of diet on human physiology and metabolism. (Author Abstract)

58. CANCER MORTALITY CORRELATION STUDIES. II. REGIONAL ASSOCIATIONS OF MORTALITIES WITH THE CONSUMPTIONS OF FOODS AND OTHER COMMODITIES.

Schrauzer GN

Univ. California at San Diego, Revelle Coll., La Jolla, CA 92093

Med Hypotheses ; 2(2):39-49 1976

The age-corrected mortalities from cancer at 17 sites were correlated with the consumptions of 12 major food items and the apparent consumptions of alcoholic beverages, cigarettes, beer, coffee, tea, and solid fuel over a 5-yr period in 17 countries. The male mortalities from cancers at all sites correlated directly with the consumption of sugar, meat, eggs, and milk and inversely with consumption of cereals. The female mortalities correlated directly and more significantly with consumptions of sugar, meat, eggs, and fat and inversely with consumption of cereal. The cancers involved in these correlations included large intestine, rectum, breast, ovary, prostate, pancreas, bladder, lung and leukemia. Cancers of the buccal cavity, pharynx, esophagus, and larynx were directly correlated with wine and alcohol consumption. Cancers of the stomach and liver were directly correlated with cereals and fish. The results are in essential accord with those of others using different statistical analyses. A modification of the diet in western industrialized nations is proposed as a means of lowering the human cancer risk. (34 refs)

59. NUTRITION AND CANCER: DIETARY DEFICIENCY AND MODIFICATIONS. (PP.153-176)

Shils ME

Cancer Epidemiology and Prevention, Current Concepts. Schottenfeld D, ed. Springfield IL, Charles C Thomas, 1976.

Extensive discussion is made of how dietary modification can influence carcinogenesis and the growth of established tumors. Nutrient intake has been demonstrated to influence tumor induction by chemicals in experimental animals. Possibly, nutritional factors influence carcinogen metabolism by host cells or by gut microflora, or host steroid metabolism is altered by dietary factors. Human epidemiological data has related dietary practices to the following types of cancer: oropharyngeal, esophageal, colon, and liver carcinomas. In the last instance, the frequent association of liver cirrhosis with hepatoma is noted: most experimental hepatocarcinogens, with the exception of urethane and diethylnitrosamine, induce cirrhosis. High fat consumption correlates with the incidences of cancers of the colon, rectum, ovary and breast and of leukemia. In general, diets low in calories inhibit the development of various spontaneous tumors in rodents but retard the establishment and growth of transplanted tumors only when stringent enough to cause host weight to diminish. Similarly, protein deprivation and other deficiencies are usually inhibitory only when food intake is decreased, with resultant poor growth or weight loss. (150 refs)

60. NUTRITIONAL MODULATION OF CARCINOGENESIS. (PP. 15-40)

Newberne PM, Rogers AE

Fundamentals in Cancer Prevention, Proceedings of the 6th International Symposium of The Princess Takamatsu Research Fund, Tokyo, 1975. The Princess Takamatsu Cancer Research Fund Tokyo Japan, 1976.

Nutrients that appear to modulate susceptibility to cancer are discussed. In New York City, patients with esophageal cancer tend to be heavy smokers with high alcoholic consumption and decreased consumption of milk, eggs, and green leafy vegetables. Dietary factors are associated with esophageal cancer in each of the areas of high incidence. Gastric cancer exhibits a high incidence in Japan, Chile, Columbia, Austria, Iceland, and Finland and a low incidence in the United States and Canada. Several dietary factors have been implicated, but studies of the food habits in gastric cancer patients have shown few significant differences in the intake of specific nutrients when compared with control groups. The incidence of colon cancer is associated with a western style diet and a higher standard of living. Hepatocarcinoma is associated with cirrhosis resulting from complex interactions of diet, toxins, and possibly viral liver disease. Increased unsaturated lipid in the diet of experimental animals results in an increased incidence of liver tumors. Induction of liver tumors is enhanced if the diet is both high in fat and deficient in the lipotropes choline, methionine, and folic acid. Breast cancer incidence is correlated with socioeconomic status and therefore with overnourishment. The incidence of breast cancer is low in developing societies and in Japanese women but increases in these population groups when they migrate to the United States. Nutrition offers an acceptable and direct means to attack the cancer problem in human populations. (83 Refs)

61. SUMMARY OF THE CONFERENCE ON NUTRITION IN THE CAUSATION OF CANCER.

Hegsted DM

Sch. Public Health, Harvard Univ., Boston, Mass. 02115

Cancer Res; 35(11Part2):3541-3543 1975

A brief summary is presented of the Conference on Nutrition in the Causation of Cancer (Key Biscayne, Fla, 1975). Many of the epidemiological associations found between diet and cancer were general ones that increased with increasing affluence and also related to heart disease. It is recommended that individuals follow more prudent diets with less fat, meat, and cholesterol, and more fruit.

62. FOOD AND DISEASES.

Knox EG

Health Services Res. Centre, Birmingham, England

Br J Prev Soc Med; 31(2):71-80 1977

Statistical correlations between the main foodstuff and nutrient intakes and the chief causes of mortality in 17 European countries and in Canada, US, and Japan were examined. Subsidiary examinations were made of the effects of including and excluding Japan and of the effects of various statistical standardization procedures. Complex food patterns were identified and related both to geographical latitude and to levels of affluence; these, in turn, were related to complex patterns of mortality. Criteria for drawing special attention to specific associations were identified, based partly on statistical significance tests and also on strength-of-association yardsticks supplied by diseases with known causes. Findings suggesting causal interpretations were (1) alcohol intakes and cirrhosis of the liver, cancer of the mouth, and cancer of the larynx; (2) total fat intakes and multiple sclerosis, cancer of the large intestine, and cancer of the breast; and (3) beer and cancer of the rectum. (25 Refs)

63. THE DIETARY ENVIRONMENT AND CANCER.

Wynder EL

American Health Foundation, New York, NY

J Am Diet Assoc; 71(4):385-392 1977

The various associations between nutritional deficiencies and cancer are reviewed. The association between heavy alcohol intake and cancer of the upper alimentary tract is discussed, along with cancer of the larynx in smokers. Data suggest that alcohol acts as a tumor enhancer and not as a carcinogen, it is also suggested that nutritional deficiencies, such as a vitamin B deficiency, make the epithelial cells more susceptible to tobacco carcinogenesis. Foods high in dietary fat have been implicated in colon cancer, while high carbohydrate-low ascorbic acid diets have been implicated in gastric cancer. Consumption of lettuce and other green vegetables and fruits apparently lowers the risk of gastric cancer. It is suggested that ascorbate inhibits nitrosamine formation thereby reducing gastric cancer risk. Dietary fat has an effect on prolactin production and release and may thus be correlated with breast cancer. Furthermore, with dietary procarcinogens accumulated in the breast fluid, prolactin modification may act as a permissive agent in the transformation process. There is a positive association between dietary fat and colon cancer. Bowel transit times may have no influence in these cases; rather, various substances in the bile acids may act as promoters for unknown carcinogens. It is suggested that a diet similar to that recommended for the prevention of cardiovascular disease may help prevent certain cancers. (51 Refs)

64. DIET AND CANCER: QUESTIONS AND ANSWERS.
Weisburger J, Hill P
NCI Conference on Cancer Epidemiology and the Clinician, Boston, MA
Cancer Suppl; 39(4):1827-1828 1977

The association between diet and cancer is discussed. The various topics include the association between fat intake and colon and breast cancer, the difference between fat-induced and carbohydrate-induced obesity, exposure to nitrogen fertilizer and upper gastrointestinal cancer, and the protective effect of either Vitamin A or E in gastrointestinal cancer. (no Refs)

65. DIET AND MORTALITY FROM MALIGNANT DISEASE IN 32 COUNTRIES.
Shennan DH, Bishop OS
No affiliation
West Indian Med J; 23(1):44-53 1974

The relationship between diet and mortality from malignant diseases was investigated in 32 countries. Data on the consumption of different types of food published by the United Nations Food and Agriculture Organization were correlated with World Health Organization data relating to deaths from carcinomas, sarcomas, lymphomas, and blood dyscrasias. The results showed three types of relationships between diet and cancer. Carcinomas of the nose and nasal sinuses were associated with deficiencies of all the main calorie-rich food types. Carcinomas of the upper alimentary tract, larynx, uterine body, thyroid, and liver were unrelated to dietary factors. All other malignant disease groups were correlated wtih the intake of one or more calorie-rich foods. Leukemia, lymphosarcoma, multiple myeloma, Hodgkin's disease and rectal, bronchial, testicular, ovarian, renal, intestinal, cervical pancreatic, breast, prostatic, and vesical carcinomas were positively correlated with fat and oil consumption. Breast cancer, lymphosarcoma, skin carcinomas, and tumors of the brain and nervous system were positively correlated with the intake of sugar, sweets, and/or total calories. The correlations between dietary factors and malignant diseases were considerably higher than the correlations between malignancy and infant mortality, percentage of the population engaged in agriculture, newsprint consumption, and gross national product. The results suggest that the sophisticated diet may serve as a vector for carcinogens of many different types which produce a variety of tumors and such a diet may facilitate the production of malignant disease in many tissues.

66. ROLE OF LIFE-STYLE AND DIETARY HABITS IN RISK OF CANCER AMONG SEVENTH-DAY ADVENTISTS.
Phillips RL
Loma Linda Univ. Sch. Health, Loma Linda, Calif. 92354
Cancer Res; 35(11/Part2):3513-3522 1975

Comparison of the mortality experience of Seventh-Day Adventist and non-Seventh-Day Adventist physicians showed equal cancer mortality, consistent with the hypothesis that the apparent reduced risk of cancer death in all Adventists might be due to selective factors. The results of a small case-control study of colon and breast cancer among Adventists showed significant relative risks for colon cancer of 2.8 for past use of meat. For current food use, the significant relative risks were 2.3 for beef, 2.7 for lamb, and 2.1 for a combined group of highly saturated fat foods. The lacto-ovo-vegetarian diet might protect against colon cancer. However, the evidence linking diet to breast cancer was less clear. Due to the marked variability in dietary habits within the Seventh-Day Adventist population, they were thought to be a productive group for further study of cancer and diet.

67. DIETARY FACTORS AND CANCER IN ISRAEL.
Modan B, Barell V, Lubin F, Modan M
Tel Aviv Univ. Medical Sch., Tel Aviv, Israel
Cancer Res; 35(11/Part2):3503-3506 1975

Risk of developing cancer is higher in the European-born Israeli population than in those originating from the Middle Eastern or North African countries. The majority of cancer sites with a higher risk in the European group involve the gastrointestinal and reproductive systems. At least some of these differences may be attributed to diet. Data based on case-control studies are provided; they indicate a high consumption of starches among gastric cancer patients and a lower fiber consumption in patients with cancer of the colon. The latter observations may be extended to cancer of the ovary, breast, and corpus uteri (assuming an interplay between the concentration of bile degradation products and hormone metabolism). Although a low fiber consumption seems a more likely mechanism, a higher fat consumption is also compatible with this model. Due to the complexity of human nutrition, it seems unwarranted to incriminate any single dietary factor in carcinogenesis. A better understanding of the metabolic pathways (coupled with consistent observations from distinct populations) must be looked for.

68. ENVIRONMENTAL FACTORS AND CANCER OF THE COLON AND BREAST.
Drasar BS, Irving D
St. Mary's Hosp. Med. Sch., London, England
Br J Cancer; 27(2):167-172 1973

Nutritional surveys using Food and Agriculture Organization data were compared with published cancer registry data to determine whether a correlation exists between living standards and diet and cancers of the breast, colon and stomach in 37 countries. Cancer of the colon was highly correlated with breast cancer; however, neither cancer was significantly associated with stomach cancer. Cancer of the stomach was not correlated with protein, fat, coloric or fiber content of the diet. Both colon and breast cancer, however, showed a high correlation with high fat and animal protein intake as well as other socioeconomic indicators of affluence.

69. ENVIRONMENTAL RISKS RELATED TO CANCER. (PP. 85-92)
Peacock PB
Cancer, The Behavioral Dimensions. Cullen JW, Fox BH, Isom RN, ed. New York, Raven Press, 1976.

Environmental risks related to the incidence of cancer are discussed. Cigarette smokers are at a greatly increased risk of lung cancer as compared with nonsmokers. Lung cancer also shows an urban excess, particularly among men; however, this has not been definitely correlated with air pollution. Asbestos is highly carcinogenic for lung cancer. Compared with the risk of cigarette smoking, the effects of occupational exposures and air pollution are small. In experimental animals, an increased uptake of fat increases the yield of breast cancer; animals on a high fat diet are also more likely to get breast cancer when exposed to chemical carcinogens. There is a strong correlation between high fat diets and increased breast cancer in women. There is a similar correlation between cancer of the colon and fat intake; cancer of the kidney and possibly of the prostate may follow such a pattern. There is probably more than one carcinogenic pathway when dealing with cancer of the colon and fat. It has not yet been proved whether there is a correlation between a lack of dietary fiber and large bowel cancer. Cholestyramine, used to reduce serum cholesterol levels by increasing the fecal loss of bile acids, may increase the incidence of colon cancer. Consumption of large amounts of salty foods and small amounts of milk may be associated with carcinoma of the stomach. Aflatoxins from Aspergillus flavus

are strongly associated with hepatic carcinoma. Nitrosamines in foodstuffs and halogenated hydrocarbons in drinking water may be carcinogenic. Estrogens, rauwolfia, alcohol, and reserpine-containing drugs may also be carcinogenic. Excess exposure to UV causes skin cancer. Psychological factors may also be associated with cancer, for example, persons with cancer of the pancreas show extreme states of depression. Priority attention should be given to modification of life-style habits that can be controlled: tobacco usage, incorrect nutrition, and alcohol usage. (49 Refs)

70. EPIDEMIOLOGY OF CANCER OF THE BREAST, STOMACH, ESOPHAGUS, LUNGS, BLADDER AND HODGKINS DISEASE.

Heyden S
Duke U. Med. Ctr., Durham, N. C.
Dtsch Med J; 20(1):3-9 1969

This is a review and discussion. Every factor which contributes to lowering of estrogen levels decreases the risk of breast cancer in women. In Japan where women have many children and usually nurse them for long periods of time the incidence of breast cancer is one-ninth that in the West. The extremely high incidence of stomach cancer in Tyrol (Austria) and Poland is attributed to consumption of large quantities of lard, the high incidence in Japan (fat-poor diet) to malignant transformation of stomach ulcers which are common in that country. Different etiologic factors are responsible for tumors in different segments of the same organ (for inst uterine cervix and corpus cancer): high incidence of esophagus carcinoma (upper third of the esophagus) in Sweden was attributed to a lack of iron and sideropenia, while the extremely frequent esophagus cancer among the Bantu in South Africa who have a very high blood iron level, is localized in the thoracal part of the esophagus. Different histology of neoplasms in the same organs can also be an expression of different etiologic factors. The dependence of cancer of the bladder on occupational factors is well established, but smoking also seems to be a causative factor. Hodgkins disease is almost unknown in people less than 50 yr old in Japan, but in older age groups its frequency is as high as in Europe or the USA.

71. EXPERIMENTAL EVIDENCE OF DIETARY FACTORS AND HORMONE-DEPENDENT CANCERS.

Carroll KK
Dept. Biochemistry, Univ. Western Ontario, London, Ontario, Canada N6A 5C1
Cancer Res; 35(11/Part2):3374-3383 1975

The current awareness of the importance of environmental factors (such as diet) in the etiology of human cancer stimulated renewed interest in animal models for studying effects of diet on tumorigenesis. Diet could influence cancer in animals by affecting the initiation or subsequent preneoplastic stage of tumorigenesis, but it had less effect on tumor growth. Caloric restriction had a general inhibitory influence on tumorigenesis. Dietary fat, on the other hand, tended to promote tumorigenesis; however, only certain types of tumors (such as mammary tumors) were affected. Both caloric restriction and dietary fat appeared to act primarily during the preneoplastic stage; their effects on hormone-dependent tumors might be mediated through changes in the hormonal environment. Variations in other dietary factors (such as protein, vitamins, or minerals) above the levels required for normal maintenance seemed to have little influence on the genesis or growth of tumors.

72. REPORT ON THE "THIRD INTERNATIONAL SYMPOSIUM ON DETECTION AND PREVENTION OF CANCER" IN NEW YORK, APRIL 26 TO MAY 1, 1976.

van der Linde F, Eppenberger U
Zurich, Switzerland
Cancer Inf; 11(3):90-94 1976

Aspects of the relation between nutrition and cancer of the esophagus and stomach, hormone-dependent tumors, biochemical markers, and viral oncology are summarized. The epidemiology of esophageal carcinoma varies by a factor of 200 between high- and low-incidence areas, but there is no uniform explanation, although vitamin A, B2, and C deficiencies have been postulated. The decreased use of nitrates as preservatives and the increased use of refrigeration could be partial explanations for the declining frequency of gastric carcinoma in western countries. The increasing frequency of colon carcinoma is attributed to high fat diets that elicit increased bile acid and cholesterol secretion, tending to favor anaerobic intestinal flora and elevated steroid catabolism. Positive correlations have been established between obesity and endometrial and breast carcinoma, perhaps associated with the conversion of androstenedione to estrone. The long-term use of estrogen derivatives is also linked to the high-risk group. The qualitative assay of specific oncofetal compounds, such as carcinoembryonic antigen and alpha-fetoprotein, is recognized as useful in the early detection of cancer, but their quantitative interpretation remains controversial. (no refs)

73. INTERDISCIPLINARY AND EXPERIMENTAL APPROACHES: METABOLIC EPIDEMIOLOGY. (PP. 485-501)

Wynder EL, Hoffmann D, Chan P, Reddy B
Persons at High Risk of Cancer: An Approach to Cancer Etiology and Control; Edited by J. F. Fraumeni, Jr. (New York: Academic Press, Inc.): 1975

The application of the multidisciplinary approach to the study of cancers of the upper alimentary and respiratory tracts and to cancer of the colon is illustrated. Epidemiologic investigations have indicated that cancer of the oral cavity, larynx, and esophagus are uniform throughout the Western world; that cigarettes, pipe tobacco, cigars, and chewing tobacco represent the principal stimulus for development; and that this stimulus is magnified by heavy alcohol consumption. A variety of tumor initiators, promoters, and accelerators in tobacco smoke have been identified, leading to the development of cigarettes having a lower carcinogenic activity than those of 25 yr ago. Alcoholism, iron deficiency, and riboflavin deficiency may have a common denominator during carcinogenesis in that they affect the activity of one of the respiratory enzymes, aryl hydrocarbon hydroxylase, which may be responsible for expressing the carcinogenic effects of polycyclic hydrocarbons. Epidemiologic studies of colon cancer indicated that it is more prevalent in the Western world, its sex ratio is near unity, its worldwide distribution is different from that of cancer of the lower rectum, its incidence is higher in the first and second generations of Japanese migrants to Hawaii and California than in Japan, and that a close correlation exists between its incidence and total fat consumption. Metabolic epidemiology supports the hypothesis that populations on a mixed Western diet, among whom the rate of large-bowel cancer is high, degrade and excrete cholesterol and bile acid metabolites to a greater degree than those populations in which the rate of colon cancer is relatively low. A number of animal studies are in progress to determine whether the quality and quantity of dietary fat and protein as well as intestinal microflora can influence the susceptibility of colon tissues to chemical carcinogens.

74. POSSIBLE MECHANISMS OF COMBINATION EFFECTS IN CHEMICAL CARCINOGENESIS.

Falk HL

Natl. Inst. Environmental Health Sciences, NIH, P.O. Box 12233, Research Triangle Park, NC 27709

Oncology; 33(2):77-85 1976

The author reviews the types of interaction mechanisms that can modify the host's carcinogenic response, thus complicating the determination of threshold levels for carcinogenesis. Variations in the extent to which a chemical will be absorbed may be due to a number of factors, including genetics. The importance of cocarcinogens in evaluating the etiology of human cancer is elucidated. The action of several promoter agents, such aliphatic hydrocarbons, phenols, carbon tetrachloride, and cigarette smoke, in this cocarcinogenic effect has been determined experimentally. Dietary factors such as fat content may also act as cocarcinogens. Microsomal enzyme induction is an important factor influencing carcinogenesis by many precarcinogens. Depending on the nature of the inducer, precarcinogen, target tissue response, and nutritional adequacy of the diet, a number of variations in response can be explained. Examples of inducible enzymes are given. Rats on protein-free diets without an inducer showed more resistance to the lethal effects of some carcinogens. Several studies showed alterations in tumor incidence resulting from interactions, for which enzyme induction with resulting enhanced detoxification was the most likely explanation. Little is known at this time about the significance of repair inhibitors on human susceptibility, except when repair is inhibited on a genetic basis. The mechanisms by which chemical carcinogens create the cancer cell remain unknown. Several laboratories have reported the induction of tumor viruses by physical and chemical carcinogens. (114 refs)

B. Specific Dietary Studies in Humans

75. INCIDENCE OF CANCER IN MEN ON A DIET HIGH IN POLYUNSATURATED FAT.

Pearce ML, Dayton S

Wadsworth Hosp. Med. Serv., VA Ctr., Los Angeles, Calif.

Lancet; 1(7697):464-467 1971

The development of cancer in 846 men participating in a study of the effects of a high polyunsaturated fat diet on atherosclerotic events was investigated. Although atherosclerotic events were more common in the group maintained on a conventional diet, an excess of non-atherosclerotic deaths was observed in the experimental diet group. The excess was accounted for by a greater incidence of fatal carcinomas in the experimental group. In the conventional diet group, 17 deaths were due to carcinoma; in the polyunsaturated fat-rich diet group, there were 31 cancer deaths. There was a higher incidence of visceral carcinomas in the experimental group than in the control group. Cancers of the lung and bronchus were the most common malignancies in both experimental and control groups, accounting for 12 deaths in the control group and 16 deaths in the experimental group. Cigarette smoking habits were not correlated with carcinoma incidence in either group to the degree of statistical significance; no non-dietary explanation suggested itself for the frequency of cancer deaths in the experimental groups.

76. CANCER AMONG MEN ON CHOLESTEROL-LOWERING DIETS: EXPERIENCE FROM FIVE CLINICAL TRIALS.

Ederer F, Leren P, Turpeinen O, Frantz ID

Natl. Heart Lung Inst., Natl. Inst. Hlth., Bethesda, Md.

Lancet; 2(7717):203-206 1971

Studies on the incidence of cancer and on cancer mortality among men on an unsaturated fat, cholesterol lowering diet were carried out in Oslo, London, Helsinki and Faribault, Minnesota. Results were compared with results obtained from a similar study carried out in Los Angeles. In the latter study an excessive cancer incidence and mortality was found among men on the cholesterol-lowering diet; the relative risk of developing cancer for men was 1.28. Studies performed in London, Helsinki and Faribault failed to confirm these results; the relative risk for cancer development among cholesterol-lowering diet patients in London, Helsinki and Faribault were 0.24, 0.78 and 0.34 resp. Results from Oslo were closer to results from Los Angeles; in Oslo the relative risk for cancer development among men on the cholesterol-lowering diet was 1.43. The close approximation of all the relative risk indices to unity suggested that a cholesterol-lowering diet does not present a clear danger of cancer development.

77. EFFECT OF HIGH AND LOW RISK DIETS FOR COLON CANCER ON FECAL BILE ACIDS AND NEUTRAL STEROLS IN MAN (MEETING ABSTRACT).

Reddy BS, Dhar AK, Vukusich D, Weisburger JH, Wynder EL

American Health Foundation, New York, NY 10021

Fed Proc; 33(3):663 1974

Epidemiological studies indicate that dietary factors in terms of high fat, high animal protein, may increase the risk of developing cancer of the colon in man. The effect of high meat (HM) and non-meat (NM) diets, representing the dietary pattern of high risk and low risk areas for colon cancer, respectively, was investigated on fecal bile acids and neutral sterol pattern, and on microbial activity in man. The fecal microflora of subjects on HM diet showed a high beta-glucuronidase activity. Fecal excretion of microbially modified bile acids and neutral sterols was decreased when subjects on an HM diet transferred to a NM diet. A strong association has been established between the level of degraded bile acids, cholesterol metabolites, beta-glucuronidase activity, and colon cancer risk among populations. All of these are diet-connected markers which may be useful in uncovering the causative factors of colon cancers in man. Other studies also indicate that a high fat (20%) intake was associated with an increased fecal bile acid and neutral sterol excretion in the rat.

78. ARE PUFA HARMFUL?

Anonymous

Br Med J; 4(5883):1-2 1973

Polyunsaturated fatty acids (PUFA), while beneficial in reducing the incidence of fatal ischemic heart disease, may promote premature aging and cancer development. In the absence of antioxidants, such as vitamin E, polyunsaturated fatty acids are liable to be oxidized to epoxides and hydroperoxides which in turn polymerize to form ceroid pigments which are thought to be atherogenic. With prudent consumption of polyunsaturated fatty acids there seems little risk of developing cancer, however, some aliphatic epoxides, the early oxidation products of the unsaturated bond, are carcinogens. It is not certain if significant amounts of these epoxides are formed within the body from unsaturated fats. Neither is it known how much vitamin E is required in man to prevent such oxidation. It is suggested that persons consuming polyunsaturated fatty acids in quantity consider taking supplements of vitamin E and should remember that saturated, monounsaturated, and polyunsaturated fatty acids should be consumed in equal amounts. It is urged that manufacturers make clearer the meaning of the term 'vegetable oils' on their labels so that consumers may avoid those oils which are particularly unsuitable for human consumption.

III. CARCINOGENS ASSOCIATED WITH FOOD LIPIDS

A. Aflatoxin and Other Natural Contaminating Carcinogens in Lipids

79. NATURALLY OCCURRING CARCINOGENS IN FOODS.

Wogan GN
Prog Exp Tumor Res; 11:134-162 1969

Substances discussed include mycotoxins (luteoskyrin and the chlorine-containing peptide from the rice mold Penicillium islandicum; aflatoxins from Aspergillus flavus or parasiticus, contaminating peanuts and other plants) and compounds from cycad seeds (cycasin), Senecio and several other species (pyrrolizidine alkaloids), cottonseed (cyclopropenoid compounds) and other food and medicinal products (including sassafras oil, ergot and griseofulvin). Most of these compounds are hepatotoxic and induce liver tumors in rats and/or mice; aflatoxin, cycasin and the pyrrolizidine alkaloids (especially lasiocarpine) are potent carcinogens. Other compounds are relatively weak carcinogens when admin alone, but show significant cocarcinogenic or tumor-promoting activity when combined with other carcinogens. Epidemiologic studies suggest a correlation between food contamination by mycotoxins (particularly the aflatoxins) and primary liver cancer in man, especially in tropical and subtropical areas. (110 refs)

80. REPORT OF THE THIRD INTERNATIONAL SYMPOSIUM ON MYCOTOXINS HELD IN PARIS ON 16-18 SEPTEMBER 1976.

van Veldhuizen CJ
Food Inspection Dept., Rotterdam, Netherlands
Voeding; 10(23):8-9 1977

The legal limits for aflatoxins and similar compounds contained in grains and oil-bearing seeds in various countries, methods of sampling and analysis, new mycotoxins, prevention of contamination, detoxification and elimination procedures, and the need for inspection of human food and animal fodder are reported briefly. (no Refs)

81. AFLATOXINS AND HEPATIC CANCER.

Payet M
No Affiliation Given
Med Chir Dig; 2:57 1975

There is some controversy about the role of aflatoxins in the pathogeny of liver cancers. The fungus Aspergillus flavus may contaminate not only the peanut but all oil-yielding plants. Industrial extraction processes guarantee the elimination of all traces of aflatoxin from cooking oils, so the role of aflatoxins can only be considered in relation to the human consumption of the residues from these processes (oil cakes). Although this consumption would seem to be equal for both sexes, primary cancer of the liver occurs five times more frequently in men than in women. In 1963, experiments showed that following the addition of a weak dose of aflatoxin to their diet, white Wistar rats developed cancer within 3 mo, after a phase of cirrhosis. These results have been achieved experimentally only in selected purebred rats. Wild rats, even in countries with high peanut and oil cake contamination, do not spontaneously develop cancer. Peanut contamination exists in all countries of the tropical zone and yet, only some of these countries have a high rate of hepatic cancer. Aflatoxins are probably not an exclusive or specific factor but just one possible factor among others in the genesis of this cancer. In conclusion, one "very curious" incident is described. During an experiment in Dakar, Senegal, in 1952, several infants of 6 to 12 mo received peanut oil cake food supplements. At the age of 7, two of these children presented definite histological alterations of the liver. A biopsy of one of them revealed a precirrhotic condition. In 1970, it was learned that one had died from a confirmed hepatic carcinoma. Reference samples of the original oil cakes were traced and found to be contaminated by Aspergillus flavus.

82. MYCOTOXICOSIS IN EUROPE IN THE 20TH CENTURY.

Berglund F
Medical Res. Dept., AB Kabi, S-104 25 Stockholm, Sweden
Lakartidningen; 72(51):5065-5066 1975

General toxicological data on mycotoxins and some statistical data on mycotoxicoses in Europe are presented. Aflatoxins have been found to be carcinogenic, and they can induce tumors in the liver, stomach, kidney, salivary glands, and intestine. Aflatoxin B1 appears to be most potent of all these compounds. In Sweden, they are present in high concentrations in peanut oil cakes and in lower concentrations in peanut butter and Brazil nuts. The max allowable aflatoxin concentration in Sweden is 600 ug/kg for fodder and 5 ug/kg for food for human consumption. (5 refs)

83. HAZARDS PRESENTED BY MYCOTOXINS AND TOXIGENIC-MOLD SPORES IN FEEDS.

Cardeilhac PT, Nair KP
Dept. Vet. Sci., Univ. Florida, Gainesville
Toxicol Appl Pharmacol; 30(2):299-308 1974

The potential hazards of mycotoxins and toxigenic-mold spores in feeds was studied. The prevalence of these was estimated using a chloroform extraction technique and detection of the toxin in the extract by bioassay for cytotoxicity; thin-layer chromatography was used to indicate the presence of aflatoxins. During one calendar year, 997 feeds were tested. Mycotoxins were obtained as either a feed lipid fraction by chloroform extraction, or a mold lipid fraction by chloroform extraction of Czapek-Dox broth after a seven day culture of mold spores present in the feed. Cytotoxicity was determined by using chick tracheal ring organ cultures. A feed sample was suspected of containing mycotoxins when both feed and mold lipids were cytotoxic; and samples were considered to contain toxigenic-mold spores when the mold lipids were cytotoxic. Aflatoxin was considered present when feed lipids were cytotoxic and contained material with fluorescent and chromatographic properties similar to the aflatoxin standard. Feed lipids comprised 1.1-3.0% of the wet weight of the samples and were assayed by suspending the lipid from 0.10 g of feed in 1.0 ml of culture medium, producing a mean lipid concentration of 1917 microg/ml. A 100% cytotoxic response was given in 16% of the lipid samples from nine basic feed types. Based on results from calculated dose-response curves, cytotoxic mold lipids which did not contain aflatoxin were more than 30 times as toxic as feed lipids, and mold lipids which contained aflatoxin were more than 300 times as toxic as feed lipids. Mycotoxin contamination was suspected in 5.7% of 749 samples with over half of the suspect samples containing aflatoxin, but this was less than 200 parts per billion. These results confirm aflatoxin as the most hazardous of the mucotoxins, although a period of storage under conditions favorable for mold growth would be necessary before contaminated feeds would present any acute hazard to livestock. The results also indicate that molds presently not considered highly toxigenic often produce toxic products and remove readily accessible required nutrients from the feed.

84. STUDY ON AFLATOXIN OF FOODSTUFFS IN TAIWAN.

Tung TC, Ling KH

J Nutr Sci Vitaminol; 14:48-52 1968

The incidence of primary liver cancer in Taiwan is very high compared to that in the United States or Europe. Liver cancer occupies 3.7 per cent of the total number of cancer cases in Taiwan and 0.2 per cent of those in the United States. Taiwan is an island surrounded by sea. The island always has a high humidity and a high temperature which enhance the growth of molds in foods. Nearly all agricultural products are dried in the field by heat from the sun and are stored in a damp storehouse. Therefore, contamination of mold metabolites in daily foods is quite common. Nowadays microbiological quality has become an important factor in determining the final quality of foods. However, little attention has been paid to possible contamination by mycotoxin such as aflatoxin in Taiwan. No policy for controlling mycotoxin such as aflatoxin has been undertaken. In addition to natural products, there is another group of food products which should be investigated for mycotoxins. Many kinds of fermentation products of rice and soybean have been used for centuries among rice eating people. The fermentative soybean products such as Japanese Miso and soybean sauce are made of soybean and rice by means of fermentation with naturally occurring molds or cultivated Aspergillus oryzae. According to our experiments, the latter mold is also able to produce a trace of aflatoxin. Its mycelia contain 0.001 to 0.01 ppm of aflatoxin.

Our first step of the study was to show whether the toxic strain of Aspergillus flavus was contaminated in our daily foods. Sixteen out of 106 food samples purchased randomly in Taipei was contaminated with the spores of Aspergillus falvus. It means that if temperature and humidity are favourable for the growth of molds, these foods might be contaminated with aflatoxin of that mold which grows on foods. The next step of our study was to investiage whether aflatoxin was really contaminated in our staple foods. Rices, sweet potatoes and peanuts are main crops in Taiwan. Fifty per cent of peanuts produced in Taiwan are used as toasted peanuts for eating. It is known that peanuts are more susceptible to Aspergillus flavus. Peanut samples were collected from 8 peanut storehouses chosen randomly by us. Three of them are contaminated with 0.32, 0.04 and 0.43 ppm respectively. Peanut butter produced in Taiwan also contained from 0.02 to 0.73 ppm of aflatoxin. Peanut cakes for animal feeding are contaminated with 0.08 to 0.29 ppm of aflatoxin. Forty to 60 per cent of peanuts are used for oil production. Peanut oil is our most popular oil and is used for cooking. In order to keep the flavor of toasted peanuts, peanut oil is put on market without refining with alkai in Taiwan. It means that if peanuts are already contaminated with the toxin, the oil produced from them are consequently contaminated with the toxin, which is fat soluble. Peanut oil samples were randomly collected from 16 peanut oil mills by us. Nine out of 16 peanut oil samples were significantly contaminated with aflatoxin. Three of them contain more than 0.05 ppm of the toxin. (Author Abstract)

85. THE CARCINOGENICITY OF ESSENTIAL OILS, FLAVORS, AND SPICES: A REVIEW.

Homburger F, Boger E

22 references

Cancer Res; 28(11):2372-2374 1968

Safrole (found in sassafras oil and as a minor constituent in many spices), which induces hepatic adenomas and hepatomas in rats, has been widely used as a flavoring agent in soft drinks and medicines. The major constituent of orange oil, D-limonene, is a skin tumor-promoting agent in mice; since the active component of D-limonene is apparently its hydroperoxide derivative, studies of the prevention of its autoxidation are recommended. Turpentine oil and eucalyptus oil also contain cocarcinogens (L-pinene and phellandrene, resp); tumor-promoting activity of other essential oils with lower terpene levels is less. Red pepper (Capsicum) induces liver tumors in rats. Many food plants contain endogenous carcinogens of the polycyclic aromatic hydrocarbon type (including benzpyrene).

86. CARCINOGENICITY OF CONTAMINANTS IN INDIGENOUS EDIBLE OILS.

Ranadive KJ, Gothoskar SV, Tezabwala BU

Cancer Res Inst., Tata Mem. Ctr., Bombay, India

Int J Cancer; 10(3):652-666 1973

Two batches of solvent-extracted ground-nut oil samples and pure argemone oil or argemone oil in combination with mustard or soybean oil were tested for carcinogenicity in two strains of inbred C17 and in inbred Swiss mice following cutaneous application, sc injection or gastric intubation. Five out of six solvent-extracted ground-nut samples (1966 batch) indigenous to India were carcinogenic by all three routes of administration in all three mouse strains, producing skin carcinomas and sarcomas and stomach tumors. A second batch of five ground-nut oils extracted with an improved food-grade n-hexane solvent in 1969 was considerably less carcinogenic than the 1966 batch. No frank carcinomas developed and no sc sarcomas were observed. None of 51 mice injected singly or multiply with pure aregemone oil and observed for their full life span developed tumors. Likewise, none of the 58 mice which received argemone oil in soybean oil and only two of 174 mice which received argemone oil in authentic mustard oil developed tumors. Soybean or authentic mustard oil alone were noncarcinogenic. However, mice treated with a local Indian market sample of mustard oil showed a weak carcinogenic response. The response was significantly increased by addition of argemone oil.

87. SANGUINARINE - A CARCINOGENIC CONTAMINANT IN INDIAN EDIBLE OILS.

Hakim SA

Sola Hakim Med. Res. Ctr., Bombay, India

Indian J Cancer; 5(2):183-197 1968

Several epidemics of edema, glaucoma, heart disease, abortions and diarrhea (sometimes fatal) in India were traced to adulteration of cooking oils by oil from the seeds of Argemone mexicana (argemone weed; yellow-flowered prickly poppy). Since the toxic alkaloid of this plant, sanguinarine (S), was also found in 49 species of 14 genera of the poppy-fumaria family, it was suggested that transmission of S by foods (especially milk from animals grazing on plants of this group which have worldwide distribution) might explain the worldwide occurrence of glaucoma. At least 4 fluorescent metabolites were isolated from the tissues of S-treated rats, 1 of which was benz(c)acridine (BcA); several experiments demonstrated that both S and BcA were complete carcinogens, inducing skin tumors in mice and bladder tumors in rats. A survey of the literature (85 refs) led to the suggestion that S is carcinogenic in man. For example, western India and Assam (where argemone weed grows wild and is used in cooking oils) and the West Indies (the original home of the plant) have the world's highest incidence of cancer of the esophagus; transmission of S by milk from animals grazing on plants of the poppy-fumaria family might also account for the high incidence of this tumor elsewhere (e.g, Bedouins of the Arab Peninsula and rural Scandinavia). It is also suggested that smoking of opium (which also contains S) might explain the high incidence of nasopharyngeal cancer in Chinese men in Singapore and in male Chinese and Filipinos in Hawaii.

B. Environmental Carcinogenic Pollutants in Lipids

88. EVALUATION OF CARCINOGENIC RISK OF CHEMICALS TO MAN. SOME ORGANOCHLORINE PESTICIDES.

International Agency for Research on Cancer
IARC Monographs; (Lyon, France) (5):241 1974

The carcinogenic risk of some organochlorine pesticides is discussed. The pesticides include aldrin, Aramite, the mixed isomers of 1,2,3,4,5,6-hexachlorocyclohexane, lindane, chlorobenzilate, 1,1,1-trichloro-2,2-di(4-chlorophenyl)ethane and associated substances, dieldrin, endrin, heptachlor, methyoxychlor, mirex, quintozene, and terpene polychlorinates. Many of these organochlorine compounds are very stable and persist in the environment. Rates of biochemical transformation vary for different compounds and different environmental circumstances, and the time necessary for a significant change in concentration may range from weeks to years. The compounds are generally only very slightly soluble in water, but they are very soluble in lipids. For this reason, they tend to be stored in animal tissues at levels that depend on the intake and the metabolic peculiarities of the species concerned. (refs)

89. PREVENTION-ENVIRONMENTAL EXPOSURE: AN OVERVIEW, INCLUDING THE ROLE OF PESTICIDES (MEETING ABSTRACT). (P. 5)

Epstein SS
Case Western Reserve University School of Medicine, Cleveland, Ohio, 44106.
Third International Symposium On Detection And Prevention Of Cancer. 1976.

There is now a strong consensus that many diseases hitherto regarded as spontaneous in origin, particularly cancer, are caused by environmental chemical pollutants. This realization is heightened by the exponential increase in exposure of the general population to currently used and new synthetic chemicals - and their degradation products in air, water, soil, and food - which, in general, are inadequately characterized toxicologically. These considerations apply with even greater emphasis to relatively uncontrolled occupational exposure to a wide range of known chemical carcinogens, in addition to a wider range still of toxicologically uncharacterized or inadequately characterized synthetic chemicals. Chlorinated hydrocarbon pesticides, such as DDT, Aldrin/Dieldrin, Chlordane and Heptachlor, are of particular interest as environmental carcinogens in view of their major usage in and around the home apart from agricultural uses, their persistence, chemical stability, ubiquity as widely disseminated contaminants of air, food, and water, lipophilicity, bioaccumulation and biomagnification in the food chain, the occurrence of residues in human fat in the part per million range, and the involuntary nature of human exposure. The carcinogenicity of these, and other related pesticides, has been unequivocally demonstrated in valid independent studies on several strains of mice. Illustratively, Dieldrin is carcinogenic at the lowest dose yet tested, 0.1 ppm, and carcinogenic effects have been induced in mice by only two months dietary exposure. While these data largely relate to hepatocarcinogenicity, as evidenced by classical morphological criteria acceptable to independent experts and by evidence of pulmonary metastases in appropriately designed test systems, other target organs are also clearly involved. More limited studies also demonstrate the carcinogenicity of these pesticides in rats. There are no available epidemiological studies which permit development of valid inferences as to the carcinogenicity of these pesticides. In a societal context, it should be noted that the efficacy of the major agricultural uses of some of these pesticides is problematic or questionable. Additionally, agricultural uses of some of these pesticides have resulted in major recognized economic losses, particularly to the poultry, animal feed, and fish industries. (Author Abstract)

90. ANALYTICAL SURVEYS OF FOOD.

Egan H, Hubbard AW
Lab. of the Government Chemist, London, England
Br Med Bull; 31(3):201-208 1975

Following a brief history of food surveillance in the United Kingdom (UK), the strategy of food contamination surveys is discussed. These consist of studies of residues in the total diet, and selective studies on individual foodstuffs. The latter are made on the basis of the importance of the foods in the national diet, their liability to pesticide exposure, and known accumulative tendencies of the foods. Organochlorine pesticide studies have noted high dieldrin levels accumulating in the fat of insecticide-dipped sheep. Argentinian beef fat samples have somewhat higher hexachlorocyclohexane and dieldrin levels than UK-produced beef fat, but lower levels of DDT-derived residues. Normally, negligible hexachlorobenzene levels are noted, while polychlorobiphenyl traces are erratic and very low. Limited surveys have also been made of other pesticide residues, including demeton- methyl , dimethoate , malathion , aldrin , bromide , and triphenyltin . Studies of toxic metals have noted an average dietary intake of 5-10 microg of mercury /day, largely determined by the fish component of the diet. The cadmium concentration of the average diet has been found to be 0.1-0.2 mg/wk; primary cadmium sources are brown body crab meat and crops grown near metal refineries. A survey of lead indicates its wider distribution in foods and higher residue levels; the daily total dietary lead intake is estimated at 0.2 mg/person (0.13 mg/kg), although canned baby food contains 0.24 mg/kg. Studies are proposed for the estimation of dietary copper , chromium , cobalt , zinc , and tin . Mycotoxin contamination is also discussed. No incidence patterns of nitrosamine presence are noted; however, cooking of protein food tends to be a source of greater secondary amines. Also, known environmental exposure levels for polynuclear aromatic hydrocarbons are relatively low, compared with those found in certain industrial atmospheres. (49 refs)

91. CHLORDANE (LETTER TO EDITOR).

Collins IS, Crawford WA
Parramatta Hosp., 158 Marsden St., Parramatta, N.S.W. 2150, Australia
Med J Aust ; 1(20):762 1976

The cases of a husband and wife, both suffering from chronic monocytic leukemia, are discussed. Study of the environmental factors revealed that both had been exposed to chlordane. The association of chlordane with hemopoietic changes is tentative. DDT, dieldrin, and BHC were present in less than av amounts in a fat biopsy of one of the patients; no traces of chemical relevant to chlordane were found. An extensive review of the literature concerning chlordane has not shown any association of chlordane or other pesticides with chronic monocytic leukemia or other neoplastic changes. (no refs)

92. EFFECT OF LONG-TERM EXPOSURE TO 1,1-DICHLORO-2,2-BIS(P-CHLOROPHENYL)ETHYLENE, TO 1,1-DICHLORO-2,2-BIS(P-CHLOROPHENYL)ETHANE, AND TO THE TWO CHEMICALS COMBINED ON CF-1 MICE.

Tomatis L, Turusov V, Charles RT, Boicchi M
Int. Agency Res. Cancer, Lyon, France
J Natl Cancer Inst; 52(3):883-891 1974

For their lifespan, 240 CF-1 mice were given 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (p,p'-DDE) or 1,1-dichloro-

2,2-bis(p-chlorophenyl)ethane (p,p'-DDE) or (DDD) at a dose level of 250 ppm or the two chemicals combined at a dose level of 125 ppm in the diet. The animals were observed until 130 wk of age, at which time the survivors in each group were killed. Exposure to p,p'-DDE resulted in a high incidence and early appearance of liver tumors, particularly in female mice. Exposure to p,p'-DDD moderately increased the incidence of liver tumors in males only and markedly increased the incidence of lung tumors in both sexes, whereas exposure to p,p'-DDE plus p,p'-DDD resulted in a marked increase in incidence and early appearance of liver tumors in both sexes. The storage levels of these metabolites were higher in fat tissue than in the liver or kidneys, and the storage concentration of p,p'-DDE was higher than that of p,p'-DDD following the same exposure levels.

93. ASSAY OF PARAFFINS AND MICROCRYSTALLINE WAXES FOR CARCINOGENIC POLYCYCLIC AROMATIC HYDROCARBONS. SECOND REPORT.

Helberg D
Dept. Food Chem., Max v. Pettenkofer Inst., Berlin
Dtsch Lebensm Rundsch; 60(11):345-347 1964

Assay technics for the identification and determination of polycyclic hydrocarbons (PHC) are presented in detail. PHC from microcrystalline waxes, 'coating' waxes and paraffins were conc with nitromethane, separated by chromatography, eluted with cyclohexane and determined by absorption spectrum (AS) fluorescence (F) analysis. With AS the sensitivity for 3,4-benzpyrene, 1,2,5,6-dibenzanthracene or 20-methylcholanthrene was 0.3 ppm; with F, it was 0.05 ppm for 3,4-benzpyrene. Antioxidants, butylated hydroxyanisole and butylated hydroxytoluene could be detected in microcrystalline waxes and paraffins by 2,6-dichlorquinone chlorimide.

C. Carcinogenic Activity Resulting from Food Processing

94. THE ROLE OF OVERHEATED FOOD FATS IN CARCINOGENESIS.

Turkiya NB, Chechelashvili GL, Krasnyanskaya PN, Beniashvili DS, Dzagnidze LN
Sci. Res. Inst. Oncol. Min. Pub. Hlth. Georgian S.S.R., Tiflis, U.S.S.R.
Vopr Pitan; 1:31-34 1971

The carcinogenicity of butter and sunflower oil heated to 160-180 C for 30-40 min was tested by po and im treatment of 260 randombred rats. P.O treatment of 100 rats consisted of 3 ml of heated oil or butter alone on alternate days for 1.5 yr or combined with 3 doses of 2 mg of benzo(a)pyrene (BP) given at 1 wk intervals at the beginning of the experiment. The im treatment (160 rats) consisted of 6 injections of natural or heated butter or oil (2 ml at 10-day intervals) alone or combined with a single dose of 1 mg of BP dissolved in benzene. No tumors occurred in the po-treated rats; 19 of 116 im-treated rats developed tumors 4 months after the beginning of the experiment. The highest incidence of tumors (5 out of 10 rats) was noticed among the animals exposed to heated butter associated with BP and no tumors occurred in the rats treated with unheated fats. The development of tumors could be attributed to the formation of thermoresistent oxidation products during the heating of the tested fats.

95. 'WARNING: BACON CAN DAMAGE YOUR HEALTH'.

Anonymous
New Sci; 70(999):300 1976

Nitrites are currently used in bacon to preserve the meat, color, and flavor and to inhibit Clostridium botulinum formation. Tests have shown that nitrosamines may be formed from nitrites and than most of the nitrosamines are found in the fat rather than the lean or rind portions. A nitrite-free bacon has been produced, but its shelf life is only 1 wk. Several authors have suggested lowering the nitrite level, but others have warned against it to prevent outbreaks of botulism.

96. POTENTIAL PRECURSORS OF N-NITROSOPYRROLIDINE IN BACON AND OTHER FRIED FOODS.

Bills DD, Hildrum KI, Scanlan RA, Libbey LM
Dept. Food Sci. Technology, Oregon State U., Corvallis
J Agric Food Chem; 21(5):876-877 1973

The possibility of producing N-nitrosopyrrolidine from several compounds in a system designed to simulate the frying of fatty foods containing small amounts of water was investigated. With the exception of tests on N-nitrosoproline, equimolar amounts of the compound to be tested and sodium nitrite were added to the system prior to heating. With a heat-up time of 10 min plus 10 min at 170 degrees, N-nitrosopyrrolidine was produced from N-nitrosoproline, pyrrolidine, spermidine, proline, and putrescine in yields of 2.6, 1.0, 1.0, 0.4, and 0.04% theoretical, resp. N-Nitrosopyrrolidine was not produced from glutamine, glutamic acid, and hydroxyproline. The occurrence of proline, spermidine, and putrescine in foodstuffs was discussed.

97. CARCINOGENICITY OF PREHEATED FATS.

Zaldivar RS
Dept. Biol., U. Chile, Santiago
Nature (Lond); 199:1300-1301 1963

Fat from guinea pigs which was preheated to 360-365C for 30 min was given by inj to groups of 6 to 11 female guinea pigs (initial av wt. 470 g) into the wall of the antrum and fundus in doses of 0.05 ml. One group sacrificed at 150 days recieved 0.1 ml into the wall of the antrum only. After periods from 16 to 240 days, 18/36 animals had developed gastric lesions (mainly focal hyperplasia of the epithelium, diverticula, and glandular infiltration of the submucosa through perforation of the muscularis mucosae). No such lesions were seen in groups of 6 to 9 (total 28) control animals given ether-extracted fat and observed from 17 to 240 days. The lesions seen in the experimental groups at the present time are not classed as precancerous, but some of them are similar to those induced by 20-methyl-cholanthrene.

98. CARCINOGENIC EFFECTS OF OVERHEATED FATS.

Vysheslavova M
Nutr. Inst., Acad. Med. Sci. USSR, Moscow
Vopr Pitan; 27(3):63-68 1968

The carcinogenic effects of heated and unheated sunflower oil (SO; 10% by wt in diet, fed throughout life) were studied in 2 groups of male rats (80g). No tumors developed in the 2 control groups (78 rats) fed unheated SO. In a 40-mo experiment in 70 rats fed heated SO (180-200 C for 5-6 hr; oxidation rate 1.0-1.5%), 6/32 rats surviving at the time the first tumor appeared (induction times were 724-1005 days) eventually developed malignant tumors (4 sc polymorphocellular sarcomas, 1 pulmonary angiosarcoma, 1 pulmonary round cell sarcoma); av survival times in treated and control rats were 8 and 16 mo, resp, but no significant differences in body wt were noted. In a 44-mo experiment in 97 rats fed heated SO (190 C for 1435 hr; oxidation rate 2.0-3.5%), benign tumors eventually developed in 2/75 rats (13.3%) surviving when the first benign tumor appeared (14 mo) and malignant tumors developed in 8/50 rats (16%) surviving when the first malignant tumor appeared (induction times were 467-1237 days). These tumors included 3 polymorphocellular sarcomas (1 sc, 1 of the large intestine, 1 widespread), 1 cavernous angioma (sc), 1 spindle cell sarcoma (sc), 1 round cell sarcoma (mesenteric lymph nodes), 1 myosarcoma (paw and abdomen),

1 leiomyoma (stomach), 1 basal cell carcinoma (paw) and 1 keratotic carcinoma (skin); 3 rats developed metastases. Other pathological findings in this group included lung abscesses (most rats), gastric ulcers (3), colloidal goiter and pleural empyema (1 each); body wt was below control levels during the first 1 yr of treatment. Both groups of rats admin heated SO also showed brown skin pigmentation and many rats developed diarrhea and edema. The total tumor incidence in both groups was 16/107 (15%) in rats surviving until the first tumors appeared.

99. CARCINOGENICITY OF HEATED FATS AND FAT FRACTIONS.

O'Gara RW, Stewart L, Brown J, Hueper WC
NCI Lab. Path., Bethesda, Md.
J Natl Cancer Inst; 42(2):275-287 1969

The urea adduct (UA), nonurea adduct (NUA), nonsaponifiable (NS) and volatile fractions of 2 commonly used vegetable fats (fresh and re-used) were tested for carcinogenicity in newborn HIH rats receiving single and multiple doses. S.c admin was used for fresh whole corn oil, the UA and NUA of heated corn oil, the NUA's of fresh or heated hydrogenated fat, the NS fraction of fresh or heated corn oil of hydrogenated fat and 2 volatile fractions of heated corn oil. P.o admin, with or without added benzopyrene (BP) was used for fresh corn oil, UA and NUA of heated corn oil and the dregs of heated hydrogenated fat (no BP); im admin was used with fresh whole corn oil, fresh and heated whole hydrogenated fat, the NUA's of fresh and hydrogenated fat and corn oil and the volatiles of heated corn oil. No tumors developed at the inj site in 864 mice inj sc with fat or fat fractions. The incidence of lymphosarcoma was zero in those given the NS fraction and 5.5% in those receiving NUA's; the incidence of lymphosarcomas and mammary fibroadenomas was similar to the spontaneous incidence. Marked deformities of the spine or submucosal cysts of the forestomach were seen in those inj sc with volatile fractions. Of 17 gastrointestinal neoplasms seen in po fat-fed rats, 10 were in those that also received BP; 30 nonalimentary neoplasms were seen in this group, but none were attributed to fat admin. The induction of sarcomas at the site of im inj of the NUA's of fresh and heated hydrogenated vegetable fat and corn oil indicates the presence of a carcinogen in these materials. This carcinogenic potential was increased with heating of the fats.

100. HEATED FATS AND ALLIED COMPOUNDS AS CARCINOGENS USING THE NEWT TEST.

Arffmann E
Dept. Path., Finsen Inst., Copenhagen, Denmark
Acta Pathol Microbiol Scand; 61(2):161-180 1964

A report containing extensive tabulations of the results of some heated and oxidated fats and a few allied compounds when applied to the back or tail of Triton cristatus or T marmoratus (both sexes). Peroxidized oil of the soybean (SBO) and ethyl linoleate hydroperoxide produced positive responses (epidermal reaction after 3-21 days) considered to be weak when compared with the sensitivity of the animals and magnitude of peroxide values (293 or 858 and 750 or 1500 m.e./kg, resp). Peroxide reduction by heat or chemical means weakened the carcinogen-like activity slightly. Epoxidized SBO, 16 alpha, 17alpha-epoxyestratrien-3-ol, commercially polymerized SBO and SBO heated at 350 C for 30-60 min had no effect. All isomers of diepoxybutane and cholestrol heated at 350 C for 1 hr produced positive reactions. It is concluded that oxidation may be considered the most important process in the transformation of lipids leading to newt-positive and, therefore, carcinogen-suspected products.

101. POLYNUCLEAR HYDROCARBON CARCINOGENS IN COOKED MEAT AND SMOKED FOOD.

Lijinsky W, Shubik P
Dept. Oncol., Chicago Sch. Med., Ill.
Ind Med Surg; 34(2):152-154 1965

The analysis of various foods and liquid smoke showed that the conc of polycyclic aromatic hydrocarbons (PAH) in bacon, smoked salmon and smoked haddock were in the range of a few parts per billion or less and most of those detected were not carcinogenic. A low conc of benz(a)pyrene (BP) was present in the smoked fish. When the conc of the hydrocarbons was determined again in charcoal-broiled steaks (see CRA 3(2): #250, 1965 for first study) purchased from a restaurant, the conc were of the same order but a little lower than those in the first analysis: BP conc was 5 microg/kg as compared with 8 microg/kg. Since analysis showed the absence of N-containing PAH, the possible contribution due to pyrolysis of the fat which dripped from the meat was assessed in fatty, charcoal-broiled barbecued ribs purchased from a restaurant. Analysis showed the following (in microg/kg): anthracene, 7.1; anthanthrene, 1.1; benz(a)anthracene, 3.6; benzo(g,h,i)perylene, 4.7; BP, 10.5; benz(e)pyrene, 7.5; chrysene, 2.2; coronene, 4.2; fluoranthene, 49; phenanthrene, 58; perylene, 1.5 and pyrene, 42. The conc of PAH was generally higher than in the steaks (e.g, BP 10.5 compared to 8 and 5 for 2 steaks).

102. CARCINOGENIC SUBSTANCES IN EDIBLE FATS AND OILS. V. STUDIES OF SAUSAGE AFTER DIFFERENT METHODS OF COOKING.

Fabian B
U. Mainz, Germany
Arch Hyg Bakteriol; 152(3):251-254 1968

The corrected conc of total aromatic hydrocarbons (AH) and carcinogenic AH in raw 'Coburger' or 'Thuringer' sausage were 11.8 and 1.5 microg/kg, resp. After pan frying, charcoal grilling, grilling over pine cones and infrared grilling, the total AH contents were 11.0, 115.0, 196.0 and 4.2 microg/kg, resp; total contents of carcinogenic AH were 7.4, 54.8, 88.5 and 0.17 microg/kg, resp. The levels of 3,4- and 9,10-benzfluoranthrene, idenopyrene and 3,4-benzpyrene increased markedly after grilling over charcoal or pine cones; these preparations were also the only ones containing 1,2-benzanthracene. It is concluded that the carcinogenic AH are formed pyrolytically and enter the sausages with the smoke.

103. CARCINOGENIC SUBSTANCES IN COOKING FAT AND OIL. VI. FURTHER STUDIES ON MARGARINE AND CHOCOLATE.

Fabian B
U. Mainz Inst. Hyg., Germany
Arch Hyg Bakteriol; 153(1):12-24 1969

Analysis of 8 samples of different margarines revealed that the content of carcinogenic aromatic compounds (1,2-benzanthracene, 3,4-benzfluoranthene, 3,4-benzpyrene, indenopyrene and 10,11-benzfluoranthene) was substantially lower (2-4 microg/kg) in brands which during manufacture had been treated with activated charcoal and steam than in untreated margarines (20-100 microg/kg). Five chocolate samples analyzed contained approx. 6 microg/kg of these substances.

IV. EXPERIMENTAL STUDIES CONCERNING LIPIDS AND FATTY ACIDS

A. Induction of Tumors with Dietary Lipids

104. PITUITARY TUMOURS INDUCED BY DIFFERENT DIETARY REGIMENS.

Vartiainen I, Heinivaara O
2nd Dept. Med., U. Helsinki, Finland
Ann Med Intern Fenn; 53(2):69-73 1964

Groups of young male Sprague-Dawley rats were fed (besides mineral and vitamin supplements) for a total of 40-80 wk the following diets: high carbohydrate (C) diet containing 80% C, 15% protein and 5% fat (17 rats); high fat diet containing 5% C, 15% protein and 80% fat (15 rats); alternating high C and high fat diets for periods of 2-8 wk. (12 rats), while the 19 controls were permitted to select their diet freely. Compared to the control animals, the groups of rats fed the diets had very large pituitaries, the largest weighing 283 mg. The enlargement of the hypophysis was due to typical chromophobe adenomas (sometimes several/gland), and these animals also had a distinctly atrophied zona glomerulosa in the adrenal.

105. RHABDOMYOSARCOMA IN MICE MAINTAINED ON FAT ENRICHED DIETS.

Szepsenwol J
Dept. of Anatomy, University of Puerto Rico School of Medicine, San Juan. P.R. 00936
Proc Am Assoc Cancer Res; 17:217 1976

The present is a study of rhabdomyosarcoma in mice of the T M strain maintained on Purina chow supplemented with refined corn oil plus free fatty acids (Group 1) and with corn oil plus estradiol dipropionate (Group 2). Purina chow was available to the mice at all times, while the corn oil plus 1.5% of fatty acids, was given to them in the amount of 200 mg per mouse daily. For the mice of Group 2, one gamma of estradiol dipropionate was added to the 200 mg of corn oil. Each tumor was divided into small fragments which were cut serially at 5 microns and stained with hematoxylin and eosin, iron hematoxylin, phosphotungstic acid hematoxylin or the trichrome method. None of the 308 controls (on Purina chow only) developed rhabdomyosarcoma. Of the 328 mice of Group one, 6, or 1.8%, developed such tumors and of the 275 mice of Group two, 8, or 2.9% developed the above malignancy. The microscopic appearance varied from one tumor to another and frequently from part to another of one and the same tumor. It was pleomorphic in one alveolar or embryonic in another. So far it is hard to decide whether dietary fat or estradiol dipropionate affect tumorigenesis directly or indirectly by activating carcinogens already present in the organism. (Author Abstract)

106. PRIMARY AND SECONDARY HEART TUMORS IN MICE MAINTAINED ON VARIOUS DIETS.

Szepsenwol J, Boschetti NV
Dept. Anatomy, Univ. Puerto Rico Sch. Medicine, San Juan, Puerto Rico
Oncology; 32(2):58-72 1975

Studies were conducted to macroscopically and microscopically examine heart tumors found in TM and C57/Bl mice on different diets. In the first group of 329 TM mice fed Purina chow supplemented with refined corn oil with free fatty acids (oleic and linoleic), one 604-day-old female developed one tumor in the heart, one in the left kidney, and five in the lungs. In the second group of 375 TM mice fed Purina chow supplemented with corn oil (without free fatty acids), a 405-day-old male developed a heart tumor and three lung tumors. These two heart tumors were both primary rhabdomyosarcomas showing cross-striated muscle fibers. The kidney and lung tumors were identified as metastases from the heart tumor. In both groups, the incidence of lung tumors, lymphosarcomas, and brain tumors was similar, while the incidence of gastric tumors was considerably lower in the second group (5%). Of the 623 controls maintained on Purina chow only, the total incidence of tumors (mainly lung) was less than 20%. One 556-day-old TM female from the second group developed a primary fibrosarcoma behind the right anterior extremity and metastases in the lung, liver, and heart. In another series of experiments, 7-day-old C57/Bl mice were inoculated sc in the interscapular region with a single dose of 30 ug of Delestrogen and maintained on Purina chow after they were weaned at 4 wk. In one male killed at the age of 533 days, metastases from a large rhabdomyosarcoma at the injection site were found in the intercostal muscles and the heart. It is suggested that a fat-enriched diet enhances the effect of a carcinogen by a mechanism that is presently unknown. (19 refs)

107. BRAIN NERVE CELL TUMORS IN MICE ON DIETS SUPPLEMENTED WITH VARIOUS LIPIDS.

Szepsenwol J
U. Puerto Rico Sch. Med., San Juan
Pathol Microbiol (Basel); 34(1):1-9 1969

The diet of T.M strain mice was supplemented with small amounts of various lipids; 95 mice developed tumors located on the upper surface of the frontal lobe, varying in diameter from 2-5 mm. Many mice had multiple tumors. The brain tumor consisted mainly of differentiated nerve cells containing neurofibrils and Nissl bodies. The type of lipid supplement and the number of tumors which developed were as follows; cholesterol, 20/80 (25%), corn oil, 1/11 (9.1%), corn oil + cholesterol, 7/22 (31.8%); mono-olein, 3/63 (4.7%); mono-olein + cholesterol, 7/64 (10.9%); monostearin, 3/53 (5.6%); mono-stearin + cholesterol, 10/72 (13.8%); lecithin, 18/73 (24.6%); and lecithin + cholesterol, 27/88 (30.6%).

108. CARCINOGENIC EFFECT OF EGG WHITE, EGG YOLK AND LIPIDS IN MICE (MEETING ABSTRACT).

Szepsenwol J
U. Puerto Rico Sch. Med., San Juan
Proc Soc Exp Biol Med; 112(4):1073-1076 1963

Incidence of malignancy in T.M nonbreeding mice maintained from the age of 4 wk on Rockland Diet (RD), RD supplemented with hard boiled egg white (RDW), supplemented with raw egg yolk (RDY), or with cholesterol and lard (RDC) was 1/20, 18/20, 19/21, and 9/19, resp. The incidence of lung adenocarcinomas for RD, RDW, RDY and RDC was 1/20, 10/20, 14/21, and 6/19, resp; that for lymphosarcomas 0/20, 17/20, 15/21, and 1/19, resp. Mammary cancers did not develop in any case. In a similar experiment where the mice were allowed to breed for 3-4 generations and the offspring were maintained on the same diets, incidence of malignancy for RD, RDW, RDY and RDC were 16/97, 130/152, 121/139, and 67/140, resp; that for lung adenocarcinoma was 10/97, 60/152, 57/139, and 26/140, resp; that for lymphosarcomas 2/97, 110/152, 98/139, and 5/140, resp; and that for mammary cancer 0/97, 0/152, 23/139, and 37/140, resp, appearing in 2-4 generations. Lung adenomas were large in RDW and RDY mice and developed at an earlier age compared to controls. When 4-6 week old RDY and RDC mice of the 3rd and 4th generation were put on RD, 8/9 and 22/35, resp, developed malignancies. Of breeding females on RDY, 23/69 developed mammary cancer, 0/68 on RDW. A carcinogen causing development of lung adenocarcinomas and lymphosarcomas is believed to be present in both egg white and yolk. The mammary gland carcinogen (present only in yolk) apparently is a lipid material. The TM strain is

considered cancer resistant, and in 15 yr of inbreeding the mice have rarely developed malignancies.

109. CARCINOGENIC EFFECT OF ETHER EXTRACT OF WHOLE EGG, ALCOHOL EXTRACT OF EGG YOLK AND POWDERED EGG FREE OF THE ETHER EXTRACTABLE PART IN MICE (MEETING ABSTRACT).

Szepsenwol J
Dept. Anat., U. Puerto Rico Sch. Med., San Juan
Proc Soc Exp Biol Med; 116(4):1136-1139 1964

T.M mice were maintained from the age of 4 wk on Rockland Diet (RD), RD supplemented with ether extract of whole powdered egg (RDEW), or with alcohol extract of raw egg yolk (RDAY), or with egg protein (whole powdered egg from which the ether extractable part had been removed; RDEP) and allowed to breed for 5-6 generations, the offspring being maintained on the same diets. Incidence of malignancy for RD, RDEW, RDAY, and RDEP was 22/138, 156/200, 179/225, and 81/112, resp; that for lung adenocarcinoma was 14/138, 77/200, 63/225, and 14/112, resp; that for lymphosarcoma was 4/138, 38/200, 35/225, and 10/112; and that for mammary cancer (in females) was 2/61, 61/96, 99/118, and 63/75, resp. The results indicate that the lipids of the egg are as carcinogenic as the whole egg and that there is more than one carcinogenic lipid present. In the case of the group fed with RDEP, the carcinogenicity was ascribed to the unextracted lipids rather than to egg proteins. For earlier studies see CRA 1(4):#662, 1963.

B. Induction of Tumors with Fatty Acids

110. INVESTIGATION OF FATTY ACIDS AND DERIVATIVES FOR CARCINOGENIC ACTIVITY.

Swern D, Wieder R, McDonough M, Meranze DR, Shimkin MB
Temple U. Sch. Med. Fels Res. Inst., Philadelphia, Pa.
Cancer Res; 30(4):1037-1046 1970

In mice admin repeated sc inj of 28 fatty acids and esters, lactones, and epoxy and peroxy compounds, inj site sarcomas were induced by 12-hydroxystearic acid, methyl 12-hydroxystearate, 4-ketostearic acid, stearohydroxamic acid, glycidyl laurate, glycidyl oleate and p-nitroperoxybenzoic acid. Lower doses of stearic acid and gamma-stearolactone also induced sarcomas. It is concluded that weak carcinogens for the sc tissue of mice occur among these classes of chemical compounds.

111. THE POSSIBLE CARCINOGENIC PROPERTIES OF ALTERED LIPIDS: A STUDY OF PURIFIED COMPOUNDS BY THE NEWT TEST.

Glavind J, Arffman E
Central Hosp., Hjorring, Denmark
Acta Pathol Microbiol Scand A; 78(3):345-350 1970

The newt test was used as a short-term test for the study of the possible carcinogenic effects of methyloleate, methyl linoleate and several of their derivatives. The substances were tested in serial dilutions in order to establish dose-response relationships. The most actively necrosis-producing compound was methyl 12-oxo-trans-10-octadecenoate. The esters of oleate and linoleate hydroperoxide and the corresponding hydroxy-compounds, obtained by reduction of the hydroperoxides, were also active. Conjugation of the double bonds in linoleic acid gave a weak activity, and the compounds obtained by trans-isomerization of the double bonds in oleic and linoleic acid were estimated as inactive. Moderate activity resulted from the introduction of a hydroperoxide or a hydroxyl group in the alpha-position to a double bond but not in the beta-position. The susceptibility of the newt to carcinogenic compounds is subject to seasonal variation, with susceptibility increasing in the fall; this factor constitutes an inconvenience attending use of the newt test for carcinogenicity.

112. CARCINOGENICITY IN MICE OF SOME FATTY ACID METHYL ESTERS. 1. SKIN APPLICATION.

Arffmann E, Glavind J
Dept. Path., Aalborg Hosp., Copenhagen, Denmark
Acta Pathol Microbiol Scand A; 82(1):127-136 1974

Two highly carcinogenic oxygen-containing derivatives of unsaturated fatty acids, methyl 12-oxo-trans-10-octadecenoate and methyl hydroxyoctadecadienoate, were applied to the interscapular skin of male and female ST/a mice, and their carcinogenic and promoting activities compared to those of methyl oleate, croton oil, and/or 7,12-dimethylbenz(a)anthracene. Both the unsaturated fatty acid derivates were potent promoters of skin papilloma induction. The genesis of malignant skin tumors was promoted by methyl oleate and oxooctadecenoate, and all three methyl esters were only weakly active as complete skin carcinogens. Systematically, all of the esters promoted the induction of malignant lymphomas, methyl oxooctadecenoate being the most active. Even without preceding initiation, this ester and methyl oleate showed some activity in lymphoma carcinogenesis. Thus, methyl oxooctadecenoate is the most active ester in the induction of tumors, its effect being essentially one of a promoter. In general, the female mice were more susceptible to the induction of skin tumors and lymphomas than the males.

113. CARCINOGENICITY IN MICE OF SOME FATTY AND METHYL ESTERS. 2. PERORAL AND SUBCUTANEOUS APPLICATION.

Kler HW, Glavind J, Arffmann E
Patologisk Institut, Aalborg sygehus Nord, Postbox 561, DK-9100 Aalborg, Denmark
Acta Pathol Microbiol Scand A; 83(5):550-558 1975

Two fatty acid methyl esters, methyl oleate (MO) and methyl-12-oxonoital-trans-10-octadecenoate (MOO), were tested for carcinogenicity by po and sc administration in male and female ST/a mice. In the experiments with po administration, MO or MOO (each 15 mg/day) was given in the diet for 300 days to previously untreated mice or to mice initially given 4-nitroquinoline 1-oxide (NQO, 1.1 mg) by stomach tube. In the other experiments, the mice received weekly sc injections of MO or MOO (equal to total doses of 0.185 or 0.025 ml) with or without previous topical application of 7,12-dimethylbenz(a)anthracene (DMBA, 50 microg). Four of 19 mice surviving 57 wk after NQO treatment alone developed a papilloma in the forestomach. Given in the diet, MOO increased the incidence of forestomach papillomas within 83 wk after initiation by NQO; the percentage of papilloma-bearing mice as well as the number of forestomach papillomas per animal was twice that seen in mice treated with NQO alone. Ingestion of MO increased the total number of papillomas, but not the relative number of tumor-bearing mice. The incidence of skin papillomas after DMBA application was not increased by the subsequent sc injections of methyl esters. The latency period was, however, lowered in mice injected with MO and, especially, with MOO in the higher total dose. Five weekly injections of MOO (0.025 ml) induced two local sarcomas in 20 female mice initiated with DMBA. In no other animals did sarcomas appear at the injection site within a 2-yr observation period. An influence of the injected methyl esters on initiated skin carcinogenesis is possible, though presumably weak. However, the results of the feeding experiments suggest a promoting potency of MOO in gastric carcinogenesis. Thus, more extensive studies should be conducted to determine the human hazard involved in dietary intake of oxygen-containing derivatives of oleic acid.

C. Modification of Chemical Carcinogenesis by Lipids and Fatty Acids

114. A COMPARISON OF THE EFFECTS OF THE HYPOCHOLESTEREMIC AGENTS, CHOLESTYRAMINE AND CANDICIDIN, ON THE INDUCTION OF INTESTINAL TUMORS IN RATS BY AZOXYMETHANE.

Nigro ND, Campbell RL, Gantt JS, Lin YN, Singh DV
Dept. Surgery, Wayne State Univ. Sch. Medicine, Detroit, MI 48104
Cancer Res; 37(9):3198-3203 1977

The effects of the ingestion of cholestyramine (2% in Purina rat chow) and candicidin (0.04%) on intestinal carcinogenesis by azoxymethane (AOM) was studied in male Sprague-Dawley rats. Groups of 20 animals were given 8 mg of azoxymethane/kg/wk for 25 wk when the study was terminated. Although each drug affects lipid metabolism differently, they increased the number of intestinal tumors over those of controls to the same degree, (av of 5 to 7.5 tumors/rat). There were no tumors in animals not injected with AOM. The cholestyramine-treated group of rats developed significantly more tumors in the large intestine than did the other groups, whereas candicidin-fed rats had the greatest number of tumors in the distal small intestine. The feces of the cholestyramine-fed animals contained more total bile acids and a greater percentage of secondary bile acids than in normal animals. In the candicidin-treated group, the feces had increased amounts of cholesterol and its metabolites and also a greater degree of cholesterol degradation. These results suggest that bile acids have a greater promoting effect on tumorigenesis in the large intestine, whereas the effect of cholesterol and/or its degradation products is greater in the distal small intestine. These findings support the concept that the carcinogenic process may vary in the different segments of the intestinal tract. (Author abstract) (23 Refs)

115. EFFECT OF DIET HIGH IN BEEF FAT ON THE COMPOSITION OF FECAL BILE ACIDS DURING INTESTINAL CARCINOGENESIS IN THE RAT.

Nigro ND, Campbell RL, Singh DV, Lin YN
Department of Surgery, Wayne State University School of Medicine, 540 East Canfield Ave., Detroit, Mich. 48201
J Natl Cancer Inst; 57(4):883-888 1976

Two groups of 20 male Sprague-Dawley rats each were given sc 8 mg azoxymethane/kg body weight and fed a normal diet or one high in beef fat. Control groups were not given azoxymethane. Fat-control animals did not excrete more total bile acids than did the normal-control group but did excrete more deoxycholic acid as the result of increased cholic acid degradation Azoxymethane itself caused an increase in fecal bile acid concentration but tended to reduce the level of cholic acid degradation. Fatty acid content in the feces increased in the animals on the fat diet but was not affected by azoxymethane. A fat-diet-dependent increase was apparent in total fecal neutral steroids and a carcinogen-dependent increase in cholesterol degradation. Dietary fat and bile steroids altered by gut microflora were important interrelated factors in the intestinal carcinogenic process of this animal model. (Author Abstract)

116. EFFECTS OF DIETARY FAT LEVEL AND DIMETHYLHYDRAZINE ON FECAL ACID AND NEUTRAL STEROL EXCRETION AND COLON CARCINOGENESIS IN RATS.

Reddy BS, Weisburger JH, Wynder EL
American Hlth. Fdn., New York, N. Y.
J Natl Cancer Inst; 52(2):507-511 1974

Studies were conducted on Fischer rats to determine the effect of dietary fat on the induction of colon tumors by 1,2-dimethylhydrazine (DMH, 10 mg/kg/ sc for 20 wk) and the effect of dietary fat and DMH on fecal excretion of acid and neutral sterols. High fat (20%) intake was associated with an increased fecal acid and neutral sterol excretion. Fecal acid sterols were more extensively degraded in rats fed a high-fat diet than in rats fed low-fat (0.5%) or normal-fat (5%) diets. DMH-treated animals excreted high levels of acid and neutral sterols and more microbially modified acid steroids than did controls. Animals fed high-fat diet and treated with DMH had a higher incidence of colon tumors and increased number of tumors/animal than did similarly treated rats on low-fat, normal-fat, or Purina Lab Chow diets. The colon tumors were adenocarcinomas invading the serosa and involving the regional lymph node.

117. DIMETHYLHYDRAZINE-INDUCED COLON TUMORS IN RATS FED DIETS CONTAINING BEEF FAT OR CORN OIL WITH AND WITHOUT WHEAT BRAN (MEETING ABSTRACT).

Wilson RB, Hutcheson DP
Univ. of Missouri, Columbia, Mo 65201
Fed Proc; 35(3):393 1976

Male rats were assigned to eight groups; four groups were given four weekly intragastric doses of sym-dimethylhydrazine (30 mg/kg) and four were given eight weekly doses. They were fed semisynthetic diets that contained either 20% beef fat or corn oil, with and without 20% wheat bran. Diets were adjusted to insure equal intake of protein and cholesterol. Based either on the total number of tumors per group or on the total number of rats with tumors animals given eight doses developed significantly more colon and small intestinal adenomas than did those given four doses. Malignant tumors of the colon, causing death, appeared earlier in rats fed corn oil as compared to those fed beef fat, but overall differences in tumor incidence and severity were not significant among rats fed different fats. Significantly fewer adenomas of the colon developed in rats fed wheat bran as compared to rats fed diets that did not contain wheat bran. However, the incidence of malignant tumors of the colon was not influenced by the dose-treatment, the type of fat or the presence or absence of wheat bran. (Author Abstract)

118. ANIMAL MODELS FOR THE STUDY OF DIETARY FACTORS AND CANCER OF THE LARGE BOWEL.

Reddy BS, Narisawa T, Maronpot R, Weisburger JH, Wynder EL
Naylor Dana Inst. for Disease Prevention, American Health Foundation, Valhalla, N.Y. 10595
Cancer Res; 35(11/Part2):3421-3426 1975

The studies in metabolic epidemiology show a strong association between dietary fat intake, level of fecal anaerobic bacteria, fecal acid, and neutral sterols and the risk of colon cancer among different populations. Current concepts visualize that colonic bile acids and cholesterol metabolites play a modifying role in large bowel carcinogenesis; these compounds are derived from dietary factors (directly or indirectly), and they subsequently are modified by the intestinal bacteria. In the animal model, 2 bile acids (lithocholic and taurodeoxycholic) act as colon tumor promoters. Rats fed a high-fat diet are more susceptible to

colon tumor induction by 1,2-dimethylhydrazine compared to animals fed a normal-fat diet. The intestinal microflora also play a modifying role in enhancing colon tumor production (by 1,2-dimethylhydrazine).

119. EFFECT OF SOURCE AND AMOUNT OF DIETARY PROTEIN AND FAT ON COLON CARCINOGENICITY OF 1,2-DIMETHYLHYDRAZINE IN RATS (MEETING ABSTRACT).

Reddy BS, Marisawa R, Sheinfil A, Weisburger JH, Wynder EL
American Health Foundation, Valhalla, New York 10595
Fed Proc; 35(3):568 1976

Epidemiologic studies suggest that high dietary fat and meat are of major importance in the etiology of colon cancer in man. We studied the effect of source and amount of dietary protein (beef and soybean) and fat (beef fat and corn oil) on the induction of colon tumors by 1,2,-dimethlhydrazine (DMH) in female Fischer rats. Weanling rats were fed one of the following diets: D1, 40% soybean protein, 25% corn oil; D2 20% soybean protein, 5% corn oil; D3, 60% freeze dried beef, 5% corn oil; D4, 25% freeze dried beef. At 50 days of age, all rats except controls received 20 s.c injections of DMH (10 mg/kg BW/wk) and autopsied 10 weeks after last injection. Animals fed D1 or D3 and injected with DMH had a higher incidence of colon tumors and developed more adenocarcinomas compared to those fed D2 or D4. The source of protein or fat had no major influence on colon cancer incidence. Rats fed D1 or D3 excreted higher levels of biliary bile acids as well as fecal bile acids and neutral sterols compared to animals fed D2 or D4. (Author Abstract)

120. EFFECT OF QUALITY AND QUANTITY OF DIETARY FAT AND DIMETHYLHYDRAZINE IN COLON CARCINOGENESIS IN RATS (MEETING ABSTRACT).

Reddy BS, Narisawa T, Vukusich D, Weisburger JH, Wynder EL
American Health Foundation, Valhalla, NY 10595
Proc Soc Exp Biol Med; 151(2):237-239 1976

The effect of quality and quantity of dietary fat on colon tumor induction by 1,2-dimethylhydrazine (DMH) was studied in weanling female Fischer rats. The rats were fed diets containing corn oil (unsaturated) or lard (saturated), at concentrations of 5% or 20%. Those fed either fat at the 20% concentration and treated with DMH had a higher incidence of colon tumors than did those fed at the 5% concentrations or those fed on control diets. Rats fed 5% corn oil had a slightly higher tumor incidence than those fed 5% lard. It is concluded that rats fed a high fat diet are more susceptible to colon tumor induction by DMH than those fed normal diets.

121. EFFECT OF A DIET WITH HIGH LEVELS OF PROTEIN AND FAT ON COLON CARCINOGENESIS IN F344 RATS TREATED WITH 1,2-DIMETHYLHYDRAZINE.

Reddy BS, Narisawa T, Weisburger JH
Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, N.Y. 10595.
J Natl Cancer Inst; 57(3):567-569 1976

Female inbred F344 rats fed diets containing high levels of beef protein and fat or high levels of soybean protein and corn oil and treated with 1,2-dimethylhydrazine had a greater incidence of colon tumors than did rats fed diets that had normal levels of such components and were treated similarly. The source of fat and protein had no major influence on the incidence of colon tumors. (Author Abstract)

122. EFFECTS OF NUTRITION AND MICROFLORA ON HEPATIC AND INTESTINAL MIXED FUNCTION OXIDASES (MFO) AND COLON CARCINOGENESIS IN THE RAT MODEL (MEETING ABSTRACT).

Martin CW, Reddy BS, Weisburger JH
Naylor Dana Inst, Valhalla, NY 10595
Fed Proc; 36(3):1148 1977

Conventional (CV) rats have a higher incidence of colon tumor induction than germfree (GF) rats when treated with dimethylhydrazine (DMH), a carcinogen requiring metabolic activation. GF rats develop a greater number of colon tumors when treated with MNNG, a direct acting carcinogen. To explain these differences, microsomal (MFO) activity was measured in liver and mucosa of large and small intestine of CV and GF rats on comparable diets and in CV rats on synthetic diets containing high and low levels of fat/protein from vegetable or animal sources. Hepatic levels of cytochrome P450 as well as aminopyrine N-demythylase and benypyrene hydroxylase were significantly higher in GF rats suggesting that these animals were in an induced state. Hepatic and intestinal MFO activity in CV rats consuming synthetic diets was generally higher with high levels of fat/protein and appeared to be significantly greater when the fat/protein diets were of vegetable origin. These results suggest that dietary and microflora modification of hepatic and intestinal MFO enzymes may play role in colon carcinogenesis. (Author Abstract)

123. FURTHER STUDIES ON METHYLCHOLANTHRENE-INDUCED TUMOURS OF THE GALLBLADDER AND LIVER IN THE GOLDEN HAMSTER.

Bain GO, Siegenberg J, Kowalewski K
Dept. Path., U. Alberta, Canada
Can J Surg; 6(3):367-371 1963

Golden hamsters fed a high cholesterol diet (addition of 2% cholesterol and 5% olive oil to basal diet) developed fatty livers and a high incidence of cirrhotic changes. In such animals the incidence of gallbladder carcinomas 53-407 days after intracholecystic implantation of 20-methylcholanthrene (20-Me) pellets (as previously described) was 83% in 24 animals, compared to 57% of 14 controls. After intrahepatic implantation of 20-Me pellets to hamsters on control or high cholesterol diet, few tumors were induced (20% and 25%, resp) and these were of the 20-Me-sarcoma type.

124. EFFECT OF SUNFLOWER OIL IN DIFFERENT DEGREES OF OXIDATION ON THE TUMOR INDUCTION IN RATS BY 2-ACETYLAMINOFLUORENE.

Vysheslavova M
Inst. Nutrit., Moscow, USSR
Vopr Onkol; 15(4):66-70 1969

Male rats were admin. N-2-fluorenylacetamide (FAA; 3.5 or 6.0 mg/day x 17 mo) alone or in combination with sunflower oil (SO; 10% of the diet, ranging in degree of oxidation from fresh state to 3.5% oxidized); 48/48 rats developed tumors within 5-8 mo, and the groups treated with 2.0-3.5% oxidized SO + FAA developed the greatest number of tumors, with more subsequent metastases, more multiple tumors, and at the fastest rate. Tumors included hepatomas, adenocarcinomas of the liver, and tumors of the skin, salivary glands and stomach. In a second experiment, rats were admin. FAA (1.2-4.0 mg/day x 12 mo) alone or in combination with SO (as above) and 67/88 rats developed tumors within 5/6 mo. Frequency, multiplicity and rate of tumor development increased as the degree of oxidation of SO increased, with similar types of tumors developing. It is concluded that preheated SO acts as a cocarcinogen with FAA in the liver; fresh SO has similar properties, but does not induce metastasis of primary tumors, as do FAA + oxidized SO, or FAA alone.

125. STUDIES ON PROMOTING ACTION IN SKIN CARCINOGENESIS.

Saffiotti U, Shubik P
Inst. Med. Res., Chicago Med. Sch.
Natl Cancer Inst Monogr; 10:489-507 1963

A number of substances were tested for carcinogenic promoting activity in Swiss mice by applying them twice weekly to the clipped dorsal skin, beginning 1 wk after a single application of 9,10-dimethyl-1, 2-benzanthracene (DMBA; 1-1.5% in mineral oil). Tests with silver nitrate (10% aqueous), iodoacetic acid (0.9% in acetone, fumaric acid (1% in acetone), ethylphenylpropiolate (5% in acetone), trihydroxymethylanthraquinone (Emodin; 0.5% in acetone), oleic alcohol, monostearin (5% in acetone) and sorbitan monolaurate were essentially negative although some of the agents produced marked epidermal hyperplasia; when a single application of croton oil (5% in mineral oil) was interspersed between the carcinogen and silver nitrate, 6/20 mice developed 14 benign tumors and 1 carcinoma. N-Dodecane showed moderate promoting activity (26 tumors, with 2 carcinomas, in 12/30 mice). Tests of several petroleum fractions showed high initial promoting activity (404 tumors, with 31 carcinomas, in 36/50 mice), but the activity disappeared on storage; while there was no carcinogenic activity in mice, in New Zealand albino rabbits the petroleum fractions alone produced considerable numbers of tumors. One application of DMBA, however, did increase tumor incidence and shorten the latent period. The hexane -eluted fraction of a methanolic extract of croton seeds (which had little vesicant activity), had all the promoting activity of the original croton oil; this could be demonstrated with urethan (20 mg/day ip for 5 days) as the initiator as well as with DMBA. In conclusion, the authors distinguish sharply between the promoting activity of compounds such as croton oil, which lead mostly to benign tumors (many of which regress spontaneously), and the additive effects of carcinogenic substances which may have a stimulatory effect on the second stage of carcinogenesis; for this additive carcinogenic effect, they suggest the term 'developing action'. Other studies on croton oil are also reviewed.

126. EFFECT OF DIETARY FAT AND DOSE LEVEL OF 7,12-DIMETHYLBENZ(A)ANTHRACENE ON MAMMARY TUMOR INCIDENCE IN RATS.

Carroll KK, Khor HT
Dept. Biochem., U. Western Ontario, London, Canada
Cancer Res; 30(8):2260-2264 1970

7,12-Dimethylbenz(a)anthracene (1, 2.5, or 5 mg po) was administered to female rats which had been maintained on a semisynthetic diet containing 20% corn oil, and to a comparison group which had received a semisynthetic low-fat diet to determine whether dietary fat has an effect on the carcinogenic efficacy of the test compound. The tumor yield (% incidence) was 7%, 57% and 93% in animals given 1, 2.5 or 5 mg of 7,12-dimethylbenz(a)anthracene, resp, with the 20% corn oil diet; with the 0.5% corn oil diet, the tumor yield was 4%, 33% and 70% resp, for 1, 2.5 or 5 mg of carcinogen administered. The type of diet fed after administration of 7,12-dimethylbenz(a)anthracene had a greater influence on mammary tumor incidence than did the type of diet fed before the carcinogen was given, indicating that the promotional stage of mammary carcinogenesis is the primary target of the low-fat effect.

127. EFFECT OF HIGH-OLEIC AND HIGH-LINOLEIC SAFFLOWER OILS ON MAMMARY TUMORS INDUCED IN RATS BY 7,12-DIMETHYLBENZ(ALPHA)ANTHRACENE.

Dayton S, Hashimoto S, Wollman J
Res. Service, Medical Service, and Lab. Service, VA Wadsworth Hosp. Center, Los Angeles, CA 90073
J Nutr; 107(8):1353-1360 1977

A mutant safflower oil, rich in oleic acid, was used for a critical test of the hypothesis that polyunsaturated fats act as co-carcinogens. Weanling female rats were each given 5 mg of 7,12-dimethylbenz(alpha)anthracene. They were then pair-fed diets containing 20%, by wt, of conventional high-linoleic safflower oil; a mutant high-oleic safflower oil; or coconut oil. Half of each group received supplementary DL-alpha-tocopherol(TC). Tumors were identified by two observers, by palpation. Data on incidence of tumors and on numbers of tumors per affected rat led to similar conclusions. At 16 wk, there were significant differences when supplementary TC was included in the diet: the group fed high-oleic safflower oil had more tumors than the group fed coconut oil. This difference was not seen in the absence of supplementary TC. When the data for TC-supplemented and unsupplemented subgroups were combined, the high-oleic safflower oil group had significantly more tumors than did the coconut oil group. The high-linoleic safflower oil group was not significantly different from either of the other groups. In all groups, histologic examination of the largest tumor in each rat revealed more benign tumors, mostly duct papillomas, than carcinomas. (Author abstract) (21 Refs)

128. SENSITIVITY OF FEEDING TESTS IN DETECTING CARCINOGENIC PROPERTIES IN CHEMICALS: EXAMINATION OF 7,12-DIMETHYLBENZ(A)ANTHRACENE AND OXIDIZED LINOLEATE.

Cutler MG, Schneider R
Med. Sch., Birmingham, England
Food Cosmet Toxicol; 11(3):443-457 1973

The sensitivity of a normal type of feeding test (Spiller's rat-cake diet) for detecting the carcinogenic risk of 7,12-dimethylbenz(a)anthracene (DMBA) to rats was compared with that of a test in which a high-fat diet containing 1% polyoxyethylene monostearate was administered and feeding of the carcinogen was begun at an earlier age. Female Wistar rats given 2.5 mg DMBA at age 6 wk and the high-fat diet showed an increased incidence of malignant mammary tumors and malignant tumors in other organs. No significant increase in malignant tumors occurred in females given a similar dose of DMBA and the normal diet. The high-fat diet also enabled the tumorigenic properties of oxidized linoleate to be detected more rapidly in female rats. An increased proportion of female rats had cervical sarcomas and mammary adenocarcinoma after addition of oxidized linoleate to their diet; in male rats the incidence of interstitial cell tumors of the testis was raised. Feeding of oxidized linoleate to CBA mice resulted in an increase in benign ovarian tumors and other benign tumors among the females. The possible risk to the population from the autoxidation of lipids is discussed.

129. INCREASED YIELD OF N-NITROSOMETHYLUREA-INDUCED MAMMARY TUMORS BY DIETARY FAT (MEETING ABSTRACT).

Chan PC, Cohen LA, Wynder EL
Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, NY 10595
Proc Am Assoc Cancer Res; 17:133 1976

The N-nitrosomethylurea (NMU)-breast cancer model described by Gullino et al (JNCI 54:401, 1975) was further

characterized in terms of (1) dose response and (2) the enhancing influence of dietary fat. Forty female Sprague-Dawley (SD) and 40 Fischer (F344) rats were given a single iv dose of NMU (50 mg/kg) at age 50 days. Two more groups (40 rats each) of each strain were given 2 x 25 or 12.5 mg/kg at ages 50 and 80 days. Each group was separated into 2 subgroups (20 rats each) and fed a high (20% lard by weight) or a low (0.5%) fat semipurified diet. After 4 months the mammary tumor yield and multiplicity showed a dose-response in both strains and was higher on the high fat diet compared to the low fat diet. SD rats were more sensitive than F344 rats to NMU carcinogenesis. This model is suitable for studying environmental effects on mammary tumorigenesis as (1) tumors were induced by a single dose of NMU, and (2) tumor development was enhanced by dietary fat. (Author Abstract)

130. EFFECT OF DIETARY FAT, ANTIESTROGEN, AND ANTIPROLACTIN ON THE DEVELOPMENT OF MAMMARY TUMORS IN RATS.

Chan PC, Cohen LA
American Hlth. Fdn., New York, N. Y.
J Natl Cancer Inst; 52(1):25-30 1974

After a single oral dose of 5 or 10 mg 7,12-dimethylbenz(a)anthracene (DMBA), female Sprague-Dawley rats fed a high fat (HF) semisynthetic diet developed mammary tumors earlier and in greater numbers than rats fed a low fat (LF) diet. The average growth rate, based on body wt, was comparable in both groups. To determine whether the dietary effect might be mediated by changes in hormones such as estrogen and prolactin, DMBA-pretreated rats fed HF and LF diets were given the antiprolactin drug CB-154 (3 mg/kg sc) or the antiestrogen drug U11,100A (1 mg/kg sc) and breast tumor incidence was measured. Whereas breast tumor development was decreased in extent and speed by the antiestrogen, the differential incidence of tumors in rats fed an HF diet remained higher in comparison to rats on a LF diet. In contrast, the antiprolactin drug completely suppressed the formation of all palpable mammary tumors at a DMBA dose of 5 mg in rats on either LF or HF diets. At a dosage level of 10 mg DMBA, not only was the tumor incidence decreased by the antiprolactin drug but the differential effect of dietary fat was abolished. The data from this study suggest that enhancement of mammary tumor growth, induced by high dietary fat, may be mediated through alterations in circulating levels of prolactin.

131. EFFECT OF HIGH FAT DIET ON SERUM PROLACTIN LEVELS AND MAMMARY CANCER DEVELOPMENT IN OVARIECTOMIZED RATS. (MEETING ABSTRACT).

Chan PC, Head JF, Cohen LA, Wynder EL
American Health Foundation, Valhalla, N.Y. 10595.
Proc Am Assoc Cancer Res; 18:189 1977

Dietary effects on serum prolactin titers and mammary tumor development in ovariectomized (ovx) rats were studied. Groups of 15 female, 50-day old Sprague-Dawley rats were ovx and fed either a high fat diet (HF, 20% lard), a low fat diet (LF, 0.5% lard), or Purina Lab Chow (PLC). There was no difference in body weight between rats fed the 3 different diets. Ether stressed serum prolactin titers in rats fed HF determined by radioimmunoassay from blood samples collected monthly in late afternoon, showed a gradual increase to 760 plus or minus 117 ng/ml (by 7th month) but remained at about 200-300 ng/ml in rats fed LF or PLC. Another 50 rats were given a single, oral dose of 5 mg 7,12-dimethylbenz(alpha)anthracene on day 50th of age. After 80 days, the rats were ovx, divided into 2 subgroups each with 3 tumor bearing rats and fed either HF or LF. Existing tumors regressed in 4-5 weeks in both subgroups but new palpable tumors appeared thereafter. Mammary cancers were observed in 15 rats on HF but in only 5 rats on LF 6 months after ovx. It is concluded that a high fat diet is able to elevate serum prolactin levels and promote breast cancer development in the absence of functioning ovaries. (Author Abstract)

132. THE ROLE OF PROLACTIN IN CARCINOGENESIS. (PP. 107-136)

Kim U
Vitamins and Hormones, Advances in Research and Applications, Vol, 34. Munson PL, Glover J, Diczfalusy E, Olson RE, ed. New York, Academic Press, 1976.

The role of prolactin in carcinogenesis is described. Epidemiological studies of mammary cancer in different races suggest the existence of genetic differences in man, but they are often obscured by demographic differences. Some have postulated differences in estrogen or androgen metabolism, while others have presumed high risk factors because plasma prolactin is elevated in near relatives of breast cancer patients. The susceptibility of mice to mammary tumor virus is highest at birth and during the nursing period and decreases with age. High dietary fat increases mammary tumor incidence in rats given chemical carcinogens. This has been attributed to elevated serum prolactin levels. Under estrogenic stimulation, the mammotropes promptly undergo hyperplasia, with increased secretion of prolactin. This is a reversible process. Regression of hypersecretion of prolactin follows cessation of estrogenic stimulation. However, if the estrogenic stimulation is uninterrupted, some prolactin cells can undergo neoplastic transformation followed by formation of prolactin-secreting adenomas. The discovery of the hypothalamic hormones and agents acting by way of the hypothalamus has emphasized the role of prolactin in mammary carcinogenesis. The triggering mechanism of mammary tumorigenesis can lie in the CNS. Prolactin appears to be the key hormone, although estrogens also are frequently involved. Prolactin acts on the plasma membrane of the mammary gland, where its instructions for growth and function of the mammary epithelium are carried out by cyclic AMP. The fact that mammary tumors cannot be induced in hypophysectomized animals in the absence of prolactin calls for reconsideration of the view that the major direct mammary carcinogens are ovarian steroids. (233 Refs)

133. NUTRITIONAL FACTORS, LONG-TERM DDT INTAKE, AND CHLOROLEUKEMIA IN RATS.

Kimbrough R, Gaines TB, Sherman JD
Commun., Dis. Ctr., U. S. Dept. Health, Educat. Welfare, Atlanta, Ga.
J Natl Cancer Inst; 33(2):215-225 1964

Male random-bred Sherman rats were fed either a purified high-fat diet (PHFD), PHFD + DDT (3.5 mg/rat/day) 6 mo later, or a purified normal-fat diet (NFD) + DDT (as above). Chloroleukemia developed in 7 animals (all less than 16 mo old), of which 4/7 were fed PHFD, 2/7 with PHFD + DDT and 1/7 with NFD + DDT. It is concluded that animals on purified diets develop leukemia; the addition of DDT to the diet has no bearing on leukemia development since leukemia was never observed in the author's experiments with DDT and other pesticides outside of these 2 studies. The leukemia was successfully transplanted and its viral origin is being investigated.

134. EFFECT OF CYCLOPROPENOID COMPOUNDS ON THE CARCINOGENIC ACTIVITY OF DIETHYLNITROSAMINE AND AFLATOXIN B1 IN RATS.

Nixon JE, Sinnhuber RO, Lee DJ, Landers MK, Harr JR
Dept. Food Sci. Technol., Oregon State U., Corvallis
J Natl Cancer Inst; 53(2):453-458 1974

The cocarcinogenic activity of cyclopropenoid fatty acids (CPFA) was investigated in Wistar and Fischer rats fed food-grade cottonseed oil (0.35% CPFA) or Sterculia foetida oil (50% CPFA) with aflatoxin B1 or diethylnitrosamine (DEN). Wistar rats fed 0.2 or 1.0 mg/kg DEN daily for an average of 7-14 months developed hepatomas with incidence rates of 40 and 70%, resp; they developed no other tumors. Wistar rats fed 20 or 100 ppb aflatoxin B1 showed hepatoma incidence rates of 0 and 43%, resp, and total tumor incidence rates of 10 and 51%, resp. The hepatoma incidence increased from 41 to 61% in male Wistar rats when CPFA was added to the 100 ppb aflatoxin B1 diets, but incidences were only 4 and 14% when CPFA was added to the low and high level DEN diets, resp. Fischer rats fed 0.1 mg/kg DEN were free of other tumors, but 7% developed hepatomas; when CPFA was added to the diet, 10% developed other tumors. The Fischer rats were more sensitive to 20 ppb aflatoxin B1 than the Wistar rats (hepatoma incidence of 21 vs 0%). The incidence of kidney tumors was less than 0.3% in all rats. CPFA exhibited a weak cocarcinogenic effect in specific comparisons, but generally did not influence the carcinogenicity of aflatoxin B1 or DEN.

135. DIETARY FACTORS WHICH MODIFY AFLATOXIN TOXICITY IN THE RAT.

Wells PA
U. California, Los Angeles, CA
Diss Abstr Int B; 34(11):5538-B 1974

Male weanling rats were maintained on diets containing 1.7 ppm aflatoxin and: no fat; saturated fat; polyunsaturated fat; or polyunsaturated fat in conjunction with low, normal or high levels of dietary protein. Aflatoxin inhibited growth in all groups except those maintained on low protein diets. Liver size varied as a function of the severity of liver tumors and was most increased in animals on normal and high-protein diets. The aflatoxin-induced increase in liver size was small in animals maintained on saturated fat diets. Liver size was not increased in rats fed low protein diets or low protein diets supplemented with cystine. Liver cholesterol levels were increased in all animals except those fed low protein diets. The elevation was greatest among those fed saturated fats; sterculic acid markedly diminished this effect. In the sterol ester and triglyceride fractions of the plasma, the C18:2/C20:4 ratio increased with a decrease in the incidence and severity of tumors. C16:0 and C18:0 decreased and C18:1 increased in the liver sterol fraction in response to aflatoxin, except in the low protein group. Aflatoxin did not produce changes in the liver triglyceride fraction, which was, however, altered in the low protein group. C18:0 was decreased and C18:1 increased in the liver phospholipid fraction in response to aflatoxin, except in the low protein group. Thus, low protein diets, and to a lesser extent saturated fat-containing diets, protect against aflatoxin toxicity.

136. HEPATOMA AND RENAL TUBULE ADENOMA IN RATS FED AFLATOXIN AND CYCLOPROPENOID FATTY ACIDS.

Lee DJ, Wales JH, Sinnhuber RO
Oregon State U., Corvallis
J Natl Cancer Inst; 43(5):1037-1044 1969

Weanling male Long-Evans rats were fed diets containing a crude aflatoxin preparation (50% B1 + 42% G1; 0.0184-0.736 ppm); some rats admin the 3 lowest doses (0.0184-0.552 ppm) also received Sterculia foetida oil, which supplied cyclopropenoid fatty acids (CPFA; 220 ppm). During the 18-mo experiment, 29/84 (34%) developed renal tubular adenomas, 8/84 (10%) showed malignant hepatomas (hepatocellular carcinomas), and 26/84 (31%) developed hyperplastic liver nodules. Admin of CPFA caused a slight but significant decrease in the growth rate; the total tumor incidence was slightly higher in the growth rate; the total tumor incidence was slightly higher in CPFA-treated rats (70%) than in rats admin aflatoxin alone (59%).

137. SYNERGISM BETWEEN CYCLOPROPENOID FATTY ACIDS AND CHEMICAL CARCINOGENS IN RAINBOW TROUT (SALMO GAIRDNERI).

Lee DJ, Wales JH, Ayres JL, Sinnhuber RO
Oregon State U., Corvallis
Cancer Res; 28(11):2312-2318 1968

In trout fed experimental diets containing aflatoxin B1 (AB; usually 0.004 ppm), the combination of cyclopropenoid fatty acids (CPFA) from Sterculia foetida oil (56 and 112 ppm CPFA) and from Hibiscus syriacus oil (210 ppm CPFA) significantly enhanced the hepatocarcinogenic effects of AB. No hepatomas developed in trout fed 2-acetylaminofluorene (100 ppm) alone for 15 mo, but addition of H syriacus oil to the diet resulted in a 20% incidence of liver tumors. The carcinogenic effects of AB were not affected by epoxyoleic acid (200 ppm; in Veronia anthelmintica oil), 5% sesame seed oil or 5% autoxidized salmon oil (peroxide value 200-300), but unusual lipid deposits were noted in the livers of fish admin sesame seed oil.

138. DIETARY FACTORS AND HEPATOMA IN RAINBOW TROUT (SALMO GAIRDNERI). II. COCARCINOGENESIS BY CYCLOPROPENOID FATTY ACIDS AND THE EFFECT OF GOSSYPOL AND ALTERED LIPIDS ON AFLATOXIN-INDUCED LIVER CANCER.

Sinnhuber RO, Lee DJ, Wales JH, Ayres JL
Oregon State U., Corvallis
J Natl Cancer Inst; 41(6):1293-1301 1968

In trout fed a commercial ration containing aflatoxin B1 (AB)-contaminated cottonseed meal (AB conc of 0.042 ppm) for 2 wk, the hepatoma incidence after 9 mo was 60%. In trout fed semipurified experimental diets containing 0.004-0.020 ppm of AB, a logarithmic dose-response relationship in the tumor incidence was seen. Addition of cyclopropenoid fatty acids (220 ppm) to the AB-containing diet (0.004 ppm of AB) markedly increased the incidence and growth of hepatoma; addition of gossypol (250 ppm) or 3-methylcoumarin (0.05 ppm) to AB-containing diets (0.004 ppm of AB) did not promote the early development of AB-induced tumors, but increased the incidence and size of the tumor nodules after 12 mo. Oxidized salmon oil and heat-polymerized corn oil did not enhance the carcinogenicity of AB.

139. INTERRELATIONSHIPS OF MYCOTOXINS WITH NUTRITION.

Hamilton PB
Dept. Poultry Science, North Carolina State Univ., Raleigh, NC 27607
Fed Proc; 36(6):1899-1902 1977

The interactions of mycotoxins with lipid, protein, carbohydrate, and vitamin nutrition are reviewed, with emphasis on aflatoxin and carcinogenicity. High-lipid diets have a mortality-sparing effect against aflatoxicosis; diets high in unsaturated fats have a growth-sparing effect. (40 Refs)

140. INFLUENCE OF POLYUNSATURATED FATTY ACIDS ON SURVIVAL OF SKIN ALLOGRAFTS AND TUMOR INCIDENCE IN MICE (MEETING ABSTRACT).

Mertin J, Hunt R
Clinical Res. Center, Watford Rd., Harrow, HA1 3UJ, Middlesex, England

Proc Natl Acad Sci USA; 73(3):928-931 1976

Preliminary studies of the effects of linoleic acid in mice were undertaken. The hypothesis that decreased polyunsaturated fatty acid serum levels should potentiate cell-mediated immune responses was tested by examining allograft survival in mice on polyunsaturated fatty acid-deficient diets. Survival of skin allografts from A strain (H-2 incompatible) and from C3H strain (H-2 compatible) mice in CBA mice was prolonged by sc or po administration of linoleic acid. Mice fed on a diet deficient in polyunsaturated fatty acids showed a relative immunopotentiation, as indicated by accelerated skin allograft rejection and decreased incidence and rate of development of methylcholanthrene-induced tumors. These observations support the hypothesis that polyunsaturated fatty acids take part in immunoregulatory mechanisms.

141. EFFECT OF DIETARY POLYUNSATURATED FAT ON THE GROWTH OF A TRANSPLANTABLE ADENOCARCINOMA IN C3HAVYFB MICE.**

Hopkins GJ, West CE
Dept of Experimental Pathology, John Curtin Sch of Med Res, The Australian National Univ, P.O. Box 334, Canberra City, A.C.T. 2601, Australia

J Natl Cancer Inst; 58(3):753-756 1977

Weanling male and female C3HA**vyfB mice were fed a low-fat (4.5%) diet until they were 60-70 days of age when they were fed high-fat (18.6%) diets containing either sunflower-seed oil (polyunsaturated fat diet) or tallow (saturated fat diet). After receiving either of the high-fat diets for 4 weeks, each mouse received an inoculum of approximately 1,700 single cells from a transplantable mammary adenocarcinoma. The cumulative incidence of tumor-bearing mice was significantly greater among both males and females fed the polyunsaturated fat diet than among males and females fed the saturated fat diet. The mean times elapsed before palpable tumors developed were less when mice were fed the polyunsaturated fat diet than when mice were fed the saturated fat diet, but these differences were not statistically significant. The cumulative incidence of tumor-bearing mice was also significantly greater among females than males. The results supported the suggestion from previous work in this laboratory that the polyunsaturated fat diet exerts its effect on the promotional stage of carcinogenesis rather than on the initial event of neoplastic transformation. (25 Refs) (Author Abstract)

142. BRIEF COMMUNICATION: ENHANCED GROWTH RATE OF TRANSPLANTED MAMMARY ADENOCARCINOMA INDUCED IN C3H MICE BY DIETARY LINOLEATE.

Rao GA, Abraham S
Veterans Admin. Hosp., Martinez, CA 94553

J Natl Cancer Inst; 56(2):431-432 1976

The effects of a diet containing linoleate on the growth rate and fatty acid composition of mouse mammary tumors were compared with those of fat-free or saturated fat diets. Three-month-old C3H female mice were given injections of 5-mg pieces of mammary adenocarcinoma and were then fed diets that either were fat free or contained saturated fat (15% hydrogenated cottonseed oil) or linoleate (1-15% corn oil). After 6 wk, the tumors in mice fed the linoleate diet weighed 3-4 times more than those in mice fed the fat-free or saturated-fat diets. Despite a linoleate-free diet, tumors contained appreciable amounts of linoleate and arachidonate (approximately equal to 2 and 9% of the total fatty acids, respectively). When the level of dietary corn oil was increased from 1 to 15%, the linoleate content of the tumors increased from 4 to 18% of the total fatty acids. However, in these instances, the tumor arachidonate levels increased to maximum values even when the 1% corn oil diet was used. These observations show that mammary tumor growth is depressed by a fat-free or saturated-fat diet and enhanced by dietary linoleate and suggest that the growth rate is related to the arachidonate content of the tumors.

143. EFFECT OF ANTIOXIDANT IN DIETS CONTAINING DIFFERENT TYPES AND AMOUNTS OF FAT ON MAMMARY TUMOR INCIDENCE INDUCED BY A SINGLE DOSE OF 7, 12-DIMETHYLBENZANTHRACENE (MEETING ABSTRACT).

King MM, Bailey DM, Gibson DD, Pitha JV, McCay PB
Oklahoma Medical Res Foundation, Okla City, OK 73104

Fed Proc; 36(3):1148 1977

Female Sprague-Dawley rats were fed diets containing either 20% corn oil, 20% coconut oil, or 2% linoleic acid, with or without 0.7% butylated hydroxytoluene (BHT). The animals were fed the diets ad libitum from 5 days of age. There were 30 animals in each dietary group. At 50 days of age, each rat was given 10 mg of 7,12-dimethylbenzanthracene (DMBA) in corn oil orally, by stomach tube. Control dietary groups were established in which no DMBA was given. The animals were examined twice each week for tumor incidence. Marked differences were noted. The incidence was highest in the animals fed the 20% corn oil diet and lowest in the 2% linoleic acid diet with the 20% coconut oil group intermediate, confirming the studies of Carroll, et al (Cancer Res 30:52, 1970; Cancer Res 27: 1737, 1967). During the course of the 200 day study, the BHT-supplemented animals showed as much as a 77% decreased tumor incidence in the coconut oil group as compared only 48% in the corn oil. The effect of BHT on the 2% linoleic acid group was significant but did not produce a greater reduction of tumor incidence than the coconut oil group. The studies indicate that polyunsaturated fat is antagonistic to the protective effect of BHT and support the hypothesis that lipid peroxidation may promote carcinogenesis by certain compounds. (Author Abstract)

144. POSSIBLE ROLES OF DIETARY FATS IN CARCINOGENESIS.

Hopkins GJ, West CE
Department of Experimental Pathology John Curtin School of Medical Research The Australian National University P.O. Box 334, Canberra City, A.C.T., 2601 Australia

Lif Sci; 19(8):1103-1116 1976

Epidemiological data have implicated dietary fat as an important factor in the aetiology of various cancers in humans. This suggestion is supported by the results of experiments with animals which have shown that increased amounts of dietary fat, in particular polyunsaturated fat, increase the incidence of some spontaneous and induced tumours. The enhancement of carcinogenesis by dietary fats appears to be exerted at the promotional stage of carcinogenesis. Changes induced by dietary fats in several biological systems involved in carcinogenesis may well indicate the underlying mechanisms responsible for the results of these experiments. These include the effects of dietary fats on the metabolism of chemical carcinogens, the structure and function of membranes, immunocompetence, DNA repair potential and endocrine function. (Author Abstract)

D. Influence of Liprotropic Deficiency on Tumor Growth and Induction

145. THE EFFECTS OF A MARGINALLY LIPOTROPE-DEFICIENT DIET ON THE HEPATIC LEVELS OF S-ADENOSYLMETHIONINE AND ON THE URINARY METABOLITES OF 2-ACETYLAMINOFLUORENE IN RATS.

Poirier LA, Grantham PH, Rogers AE
Carcinogen Metabolism and Toxicology Branch, National Cancer Institute, NIH, Bethesda, Maryland 20014
Cancer Res; 37(3):744-748 1977

Hepatic levels of S-adenosylmethionine (AdoMet), of glutathione, and of the microsomal enzymes p-nitroanisole demethylase and benzo(a)pyrene hydroxylase were measured in male and female rats fed a diet marginally deficient in choline and methionine and void of folic acid (lipotrope deficient) or an adequate diet for 0 to 14 weeks with and without added 2-acetylaminofluorene (AAF). The urinary metabolites of AAF were determined throughout the experimental period. After 2 to 4 weeks of dietary administration, the hepatic AdoMet levels were 43% lower in male rats fed the lipotrope-deficient diet than in male rats fed the lipotrope-adequate diet; no differences were found in hepatic AdoMet of females fed the lipotrope-deficient or lipotrope-adequate diets for 2 to 14 weeks. Administration of AAF to lipotrope-deficient female rats for 2 weeks led to a transient decrease in hepatic levels of AdoMet. The administration of AAF for 2 to 14 weeks did not significantly affect hepatic AdoMet in female rats fed the lipotrope-adequate diet or in male rats fed either diet. Female rats fed the lipotrope-deficient diet and treated with AAF excreted decreased proportions of N-hydroxy-2-acetylaminofluorene and increased proportions of 5-hydroxy-2-acetylaminofluorene in their urine. However, the urine of lipotrope-deficient male rats treated with AAF contained increased proportions of N-hydroxy-2-acetylaminofluorene and decreased levels of 5-hydroxy-2-acetylaminofluorene. The urinary excretion of 7-hydroxy-2-acetylaminofluorene by male and female lipotrope-deficient rats treated with AAF was generally similar to that in lipotrope-adequate rats. The lipotrope-deficient diet did not appear to alter the hepatic levels of glutathione, p-nitroanisole demethylase, or benzo(a)pyrene hydroxylase in male or female rats. Benzo(a)pyrene hydroxylase activity was lower in the livers of lipotrope-deficient male rats treated with AAF for 8 to 14 weeks than in the livers of lipotrope-deficient rats not receiving the carcinogen. The altered metabolism of AAF correlated well with the previously reported effects of a marginal lipotrope deficiency on AAF carcinogenesis. (Author Abstract)

146. REDUCTION OF N-NITROSODIETHYLAMINE CARCINOGENESIS IN RATS BY LIPOTROPE OR AMINO ACID SUPPLEMENTATION OF A MARGINALLY DEFICIENT DIET.

Rogers AE
Department of Nutrition and Food Science, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139
Cancer Res; 37(1):194-199 1977

In studies in this and other laboratories, induction of hepatocarcinoma by several different chemical carcinogens was enhanced in rats fed diets deficient in lipotropes (choline, methionine, folic acid), amino acids, and niacin, and high in fat. In some cases, specific supplementation with lipotropes blocked carcinogenesis. In studies reported here, specific supplementation of a marginally deficient diet that enhanced carcinogenesis in rats, with the amino acids or lipotropes in which it was deficient, significantly decreased induction of hepatocarcinoma by N-nitrosodiethylamine. Niacin supplementation decreased hepatocarcinoma incidence only slightly; the addition of beef fat to an adequate diet did not enhance tumor induction. Rats fed the amino acid- or lipotrope-supplemented diets had an increased incidence of hepatic hemangioendothelial sarcomas, compared to deficient rats or to rats fed the adequate control diet. Methionine was contained in both the amino acid and the lipotrope supplement and probably was responsible for reducing hepatocarcinoma incidence. Methionine has been found to have an anticarcinogenic effect in other studies and also to block the depletion of hepatic folate stores that is induced by N-nitrosodiethylamine. Interactions between carcinogens, S-adenosylmethionine, and folate may be significant in hepatic or other tissue carcinogenesis. One or more hepatic microsomal oxidases were depressed in rats fed any of the high-fat diets but were not correlated with tumor incidence. (Author Abstract)

147. FACTORS MODIFYING CARCINOGENESIS. (PP. 7-12)

Newberne PM
Onco-Developmental Gene Expression. Fishman WH, Sell S, ed. New York, Academic Press Inc, 1976.

Dietary factors modifying carcinogenesis are reviewed. Talc, asbestos, and high consumption of raw vegetables have been associated with the high incidence of gastric cancer in Japan. Diets high in protein and/or fat and low in fiber are consumed by populations having a high incidence of colon cancer. A diet high in fat and marginal in lipotropes increased colon carcinoma from dimethylhydrazine in rats. Primary liver cancer is a major problem in some populations of Africa, south China, Hawaii and Thailand. Among the Bantu, the age specific incidence is 500-fold that in the United States. In rats, a high fat diet deficient in choline and methionine enhances chemical carcinogenesis in the liver. (29 Refs)

148. DIETARY EFFECTS ON CHEMICAL CARCINOGENESIS IN ANIMAL MODELS FOR COLON AND LIVER TUMORS.

Rogers AE, Newberne PM
Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, Mass. 02139
Cancer Res; 35(11/Part2):3427-3431 1975

The studies of dietary effects on chemical carcinogenesis in rats demonstrate that colon tumor induction is enhanced by increased dietary fat intake or dietary deficiency of vitamin A (in some but not all cases). The enhancing effect of a high-fat diet is augmented by lipotrope deficiency. Induction of hepatic tumors by several different carcinogens is also enhanced in rats fed a high-fat diet marginally deficient in lipotropes. The dietary effects may be exerted through alteration of metabolism of carcinogens, which is demonstrated in lipotrope-deficient rats, through immunological mechanisms, which influence induction of colon tumors, or through effects on gastrointestinal bacteria and bile acid metabolism. Demonstration of dietary effects on carcinogenesis may require utilization of combined dietary stresses that alter metabolic loads but do not impair growth seriously.

149. VARIABLE EFFECTS OF A LIPOTROPE-DEFICIENT, HIGH-FAT DIET ON CHEMICAL CARCINOGENESIS IN RATS.

Rogers AE
Department of Nutrition and Food Science, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139
Cancer Res; 35(9):2469-2474 1975

Earlier studies demonstrated enhanced chemical carcinogenesis in the liver, colon, and probably esophagus of

male rats that were fed a lipotrope-deficient, high-fat diet. In further experiments, designed to examine the range of the dietary effect on chemical carcinogenesis, rats were fed either the marginally lipotrope-deficient, high-fat diet or an adequate control diet, and treated with N-2-fluorenylacetamide, 3,3 diphenyl-3-dimethylcarbamoyl-1-propyne, N-methyl-N-nitroso-N'-nitroguanidine, N-(4-(5-nitro-2-furyl)-2-thiazolyl)formamide, aflatoxin G1, or ethionine. N-2-Fluorenylacetamide induced hepatocarcinomas more rapidly and in higher incidence in deficient rats than in control rats. 3,3-Diphenyl-3-dimethylcarbamoyl-1-propyne induced a higher incidence of hepatocarcinomas but not gastric tumors in deficient rats. Aflatoxin B1, included as a positive control, was significantly more hepatocarcinogenic in deficient rats. Gastric tumor induction by N-methyl-N-nitroso-N'-nitroguanidine and induction of tumors of the urinary bladder by N-(4-(5-nitro-2-furyl)-2-thiazolyl)formamide were not influenced by diet. Aflatoxin G1 and ethionine were toxic to deficient rats, and carcinogenic doses could not be administered. (Author Abstract)

150. DIETARY ENHANCEMENT OF INTESTINAL CARCINOGENESIS BY DIMETHYLHYDRAZINE IN RATS.

Rogers AE, Newberne PM

Dept. Nutrition and Food Sci., Massachusetts Inst. Tech., Cambridge

Nature (Lond); 246(5434/5435):491-492 1973

Male Sprague-Dawley rats were fed a semisynthetic diet which was either adequate in all known respects (diet 1) or high in fat and marginally deficient in the lipotropes, choline,and methionine (diet 2). After 3 weeks, half the rats on each diet were given ten doses of 30 mg/kg/week of dimethylhydrazine (DMH) intragastrically over 14 weeks, while the rest were given 5 similar doses over 7 weeks. All animals became moribund or died from intestinal carcinoma, with both diet and dose of DMH influencing the length of time between the first dose of DMH and death from intestinal carcinoma. Diet 2 rats given the larger amount of DMH began to die with tumor 17 weeks after initiation of treatment, and the curve rose steeply with time; diet 2 rats given the smaller amount of DMH began to die with tumor after 18 weeks, but the curve rose less steeply. Diet 1 rats given the larger amount of DMH began to die with tumor after 21 weeks, and the curve rose steeply with time; diet 1 rats given the smaller amount of DMH began to die after 23 weeks, and the curve rose less steeply. The rats fed the normal diet were also more susceptible to tumors of the ear duct, with those given the larger amount of DMH showing a higher incidence. Thus lipotrope deficiency enhanced the DMH induction of colonic carcinoma, while offering some protection against the DMH induction of ear duct carcinoma; no significant effect of diet on carcinogenesis in the small intestine was noted. The data suggest that the dietary effect is exerted in the colon itself, either directly on the mucosa or indirectly by altering bacterial flora and its metabolism of the carcinogen.

151. DIET AND AFLATOXIN B1 TOXICITY IN RATS.

Rogers AE, Newberne PM

Dept. Nutr. Food Sci., Massachusetts Inst. Tech., Cambridge

Toxicol Appl Pharmacol; 20(1):113-121 1971

Sprague-Dawley and Fischer male weanling rats were maintained on either an adequate diet or a marginally lipotrope -deficient diet. Aflatoxin B1 (AFB1) was administered ip one or more times or by gastric intubation (i.g route); in addition, some rats were given protective compounds i.g. (including mercaptoethylamine (MEA), vitamin K, menadione and alpha-tocopherol). The rats were starved overnight before killing and were given tritiated thymidine (ip) before death. The object was to examine the influence of diet on the toxicity of a single or repeated doses of AFB1. The deficient diet protected rats against a 7-9 mg/kg dose of AFB1. This dose was lethal to 60-100% of those rats given the adequate diet; 20% of the unaffected rats showed areas of abnormal hepatocytes, probably preneoplastic in composition. These results were only obtained in rats receiving one dose of AFB1 since it was discovered that rats on the deficient diet were highly sensitive to repeated doses of AFB1. In all cases, none of the protective compounds tested had any discernible effect. In fact, enhancement of AFB1 toxicity by MEA was observed. Necrosis was found to varying degrees when histological studies were done on affected livers. Proliferation of bile duct cells was common, as was an increase in the size of periportal hepatocytes and focal hyperplasia. Resting levels of drug-metabolizing enzymes were low in livers of deficient rats and did not change in response to AFB1 as did the same enzymes in rats fed the adequate diet. This suggests that metabolic products of AFB1 are involved in both its toxicity and its carcinogenicity.

152. NUTRITION AND AFLATOXIN CARCINOGENESIS.

Rogers AE, Newberne PM

Dept. Nutr. Food Sci., Massachusetts Inst. Technol., Cambridge

Nature (Lond); 229(5279):62-63 1970

Interactions between nutritionally induced liver disease and carcinoma induced by aflatoxin were investigated. Diets marginal in lipotropes were associated with differences in the response of rats to aflatoxin. Male rats were maintained on a lipotrope-deficient diet or on a control diet; for acute toxicity studies rats were given a single ip dose of aflatoxin B1 (7 mg/kg). The lipotrope deficiency protected all rats against doses of aflatoxin which were lethal to 60-100% of rats on the control diet. Rats on the lipotrope-deficient diet and a carcinogenic dose of aflatoxin B1 (15 daily doses of 25 microg each) showed focal areas of hyperplastic abnormal hepatocytes which were thought to be preneoplastic. A close correlation was also observed between the early appearance of liver cell carcinomas and the lipotrope-deficient diet. Carcinomas had appeared in 25% of rats on the lipotrope-deficient diet 6 months after aflatoxin treatment, and in none of the rats on the normal diet at this point. The lipotrope-deficient diet decreased aminopyrine demethylase, p-nitroanisole dimethylase, and benzpyrene hydroxylase activities relative to the values for these enzymes in rats on the control diet. The findings may indicate that aflatoxin B1 is not itself toxic, but must be metabolized to a toxic product, a process which normally-nourished livers accomplish readily, but which lipotrope-poor livers do not; the high tumor incidence in areas in which there is malnutrition and aflatoxin B1 food contamination tend to support this hypothesis.

153. AFLATOXIN B1 CARCINOGENESIS IN LIPOTROPE-DEFICIENT RATS.

Rogers AE, Newberne PM

Massachusetts Inst. Tech., Cambridge, Mass.

Cancer Res; 29(11):1965-1972 1969

Beginning at 6 weeks of age male Fischer rats were fed either a lipotrope-deficient diet or a control diet inducing borderline lipotrope deficiency. Aflatoxin B1 (A; 25 microg/day for 5 days/week x 3 weeks or 1/week x 15 weeks; total dose 375 microg) was admin by gastric intubation to both groups at 18 weeks of age. Rats were sacrificed from 24 hours to 1 yr after the last A dose. Deaths in animals on the control diet appeared to be from hepatocarcinomas in all cases; deficient rats had no hepatocarcinomas at death. Malignant hepatic tumors were first found in sacrificed rats from both diets at 6 mo, and by 12 mo incidence was 100% in both

groups. An early hyperplastic hepatocytic response was seen in control diet animals, and it persisted to time of carcinoma development; it was not found in deficient animals.

154. THE INFLUENCE OF A LOW LIPOTROPE DIET ON RESPONSE OF MATERNAL AND FETAL RATS TO LASIOCARPINE.

Newberne PM
MIT, Cambridge, Mass.
Cancer Res; 28(11):2327-2337 1968

Several groups of Charles River (caesarean-derived) female rats were fed low-lipotrope diets (choline-and vitamin B12 -free) or control diets from day 1 of pregnancy, and treated with 1 or 2 po doses of lasiocarpine (L) on day 13-17 of pregnancy. In 1 group (admin. 75 mg/kg of L on day 14), liver necrosis was seen in the offspring but not in the mothers; the offspring showed significant pathological changes in the liver at age 7 wk. In the other groups, liver necrosis was seen in both the mothers and the newborn offspring. The low-lipotrope diet enhanced the effects of L on both the maternal and the fetal liver.

155. HYPERPLASTIC AND EARLY NEOPLASTIC LESIONS OF THE LIVER IN RATS OF VARYING AGES WITH DIETARY-INDUCED CIRRHOSIS.

Reuber MD
NCI, Bethesda, Md.
Tumori; 55(2):79-82 1969

Male and female inbred Buffalo-strain rats, 4-52 weeks old, were given a high-fat, low-protein diet, deficient in choline. The most advanced lesions were in the 8-week-old male animals (16 rats), 2 with hepatocellular carcinoma, and 14 with hyperplastic nodules. All the female 4-week-old (13), and half the 8 and 24-week-old rats (9-10) had hyperplastic nodules, with one hepatocellular carcinoma developing in the latter 2 groups. Most of the animals with nodules had moderate or severe cirrhosis. The hyperplastic lesions, in periportal regions, were similar to precarcinogenic lesions in animals treated with chemical carcinogens.

156. CONCLUDING REMARKS ON GENE EXPRESSION AND CELL CYCLE CONTROL. (PP. 89-90)

Leffert H
Onco-Developmental Gene Expression, Papers Presented at a Conference Sponsored by the International Research Group for Carcinoembryonic Proteins, and Held at San Diego, May 29-June 1, 1976. International Research Group for Carcinoembryonic Proteins San Diego California, 1976.

Dietary intake is a potent modifier of the loss of proliferation control. In choline-deficient rats exposed to chemical carcinogens, altered endocrine patterns that mimic changes observed during liver regeneration induced by partial hepatectomy are observed. Therefore, lipotrope-deficient conditions may reregulate steady-state tissue metabolism so as to either enhance initiation and/or progression of carcinogenesis. Purines such as hypoxanthine and inosine are also known to be involved in the promotion of DNA synthesis as shown by studies in cultured hepatocytes. A highly phosphorylated ^{3}H-hypoxanthine-derived, adenine-containing compound has been identified as a possible regulatory nucleotide in rat liver. Changes in the rates of proliferative transitions have been shown to be dependent on a number of internal regulatory mechanisms. Increased transport of nuclear RNA into the cytoplasm occurs during hepatic regeneration, G0 and G1 to S transitions. Involvement of phosphorylated, nonhistone chromosomal proteins has been suggested as a requisite for S-phase transcription of histone genes; nuclear protein kinases may perform these processes. DNA polymerases alpha and a 6S form may be directly involved in the initiation. (0 Refs)

157. MODIFICATIONS OF CARBOHYDRATE METABOLISM OBSERVED DURING HEPATOCARCINOGENESIS BY DIMETHYLAMINOAZOBENZENE. I. STUDIES ON GLYCOGEN METABOLISM.

Meunier M, Jacob A
Res. Ctr. on Normal and Cancerous Cells, 94-Villejuif, France
Int J Cancer; 3(4):454-459 1968

In male Sprague-Dawley rats fed a choline-and lactalbumin -free + 10% fat diet (diet X) or a choline-free diet containing 6% fat and 5% lactalbumin (diet CY), supplemented by 4-dimethylaminoazobenzene (DAB; 0.06%), hepatomas of similar histology appeared after 8-12 or 4-8 mo of treatment, resp. Controls were fed diets X or CY containing choline. Glycogen metabolism was studied in the liver tumors and adjacent noninvaded areas. The hypoglycemia during slow or rapid tumor invasion differed in origin with the fat content of the diet; with the higher lipid conc. (diet X) glycogen storage increased, but this was not hydrolyzed to furnish blood glucose; with the lower fat conc. (diet CY), the glycogen reserves disappeared. Thus, the glycogenic function was unstable; glycogenesis was depressed by low fat and the rate of glycogen breakdown was retarded by high fat in the diet. The only significant differences between the control groups were in glycogen synthetase (higher with diet CY) and phosphorylase conc. (higher with diet X); differences in blood glucose (normal), glycogenesis, liver content of glucose-6-phosphate and phosphoglucomutase levels were not significant.

158. MODIFICATIONS OF CARBOHYDRATE METABOLISM OBSERVED DURING HEPATOCARCINOGENESIS BY DIMETHYLAMINOAZOBENZENE. II. MODIFICATION OF THE RELATIVE ROLE OF THE EMBDEN-MEYERHOF PATHWAY.

Jacob A
Fac. Sci., Paris
Int J Cancer; 3(4):460-466 1968

Liver enzymes of the Embden-Meyerhof pathway were studied in male Wistar rats during hepatoma induction by 4-dimethylaminoazobenzene (DAB; 0.06%) in choline-free diets containing 10% fat and no lactalbumin (diet X) or 6% fat and 5% lactalbumin (diet CY). Controls were fed diets X or CY containing choline. In controls on diet X, liver tissue respiration was decreased 27% and glycolysis increased 20%. Glucokinase, hexokinase and phosphofructokinase increased 20%, 47% and 53%, resp, with a slight (14%) reduction in pyruvate kinase. Rapid tumor invasion, especially in the early stages of DAB admin, was accompanied by a reduction of all enzymes except hexokinase; rats on the low-fat diet (CY) were more sensitive to DAB. Comparison of glucokinase and phosphofructokinase activity with glucose-6-phosphatase and fructose-1, 6-diphosphatase showed carbohydrate breakdown overcoming carbohydrate formation during invasion of the liver by tumor cells. During this process, a larger proportion of the carbohydrates was mobilized by the pentose phosphate pathway.

E. Distribution of Lipids and Fatty Acids in Neoplastic Tissues or Cells

159. MAJOR LIPID CLASSES IN PLASMA MEMBRANE ISOLATED FROM LIVER OF RATS FED A HEPATOCARCINOGEN.

Perkins RG, Kummerow FA
Mayo Clinic and Medical Sch., Rochester, MN 55901
Biochim Biophys Acta; 424(3):469-480 1976

More phosphatidylethanolamine and less phosphatidylinositol were present in the lipid of plasma membrane isolated from the liver of male Sprague-Dawley rats fed a diet containing the hepatocarcinogen, N-2-fluorenylacetamide, than were present in the lipid of plasma membrane isolated from the liver of rats fed the basal diet. Phosphatidylcholine, phosphatidylethanolamine, and sphingomyelin from the former membranes had relative amounts of 18:1 in their fatty acyl profiles that were 1.5-1.7 times the relative amount of 18:1 in the same phospholipid from the latter membranes. Furthermore, the former membranes contained 1.3 times more cholesterol and 1.35 times more sphingomyelin than the latter membranes. It cannot be concluded or implied that these changes in the lipid composition of the plasma membrane in the rats fed the carcinogen were part of the early stages of carcinogenesis.

160. DISTRIBUTION OF GEOMETRICAL AND POSITIONAL ISOMERS OF OCTADECENOATE DERIVED FROM INDIVIDUAL LIPID CLASSES OF LIVER AND HEPATOMA.

Wood R, Chumbler F, Wiegand RD
Univ. of Missouri Sch. Medicine, Columbia, MO 65201
J Am Oil Chem Soc; 53(2):149A 1976

Groups of rats were inoculated with minimal deviation hepatoma 7288CTC and placed on one of four diets consisting of: a fat free diet supplemented with either 0.5% safflower oil (diet A), 15% safflower oil (diet B), 15% safflower oil free fatty acid (diet C), or 15% partially hydrogenated safflower oil free fatty acids (diet D). After 4 weeks the animals were sacrificed, hepatomas and livers removed, and the lipids were extracted and fractionated into individual lipid classes. Octadecenoate fractions were isolated from cholesteryl esters, triglycerides, phosphatidylethanolamines, and a phosphatidylcholines and analyzed quantitatively for geometrical and positional isomer content. The octadecenoate fraction from diet D consisted of 66% trans and 33% cis isomers. The octadecenoic fraction of cholesteryl esters, triglycerides, phosphatidylethanolamines, and phosphatidylcholines isolated from both hepatoma and liver of animals on diets A, B, and C was greater than 95% the cis isomers. C-18 monoenes of triglycerides, cholesteryl esters, phosphatidylcholines, and phosphatidylethanolamines from liver of animals fed diet D consisted of 12, 27, 46, and 72% trans isomers, respectively. In contrast, the octadecenoate fraction of all lipid classes from hepatoma of animals on diet D contained the same approximate trans isomer content (15-20%). The positional isomers of both the cis and trans fractions from diet D ranged from D9 to D14. The cis octadecenoate fraction from all classes of both liver and hepatoma from animals fed diets A, B, and C consisted of predominately the D9 and D11 isomers, but the quantity of the two isomers differed among lipid classes and between liver and hepatoma. In contrast to the high cis, D10, octadecenoate content of dis D, all lipid classes of both liver and hepatoma contained very small quantities of this isomer. The positional isomeric composition of trans octadecenoate from hepatoma and liver triglycerides and cholesteryl esters was similar to diet D. In contrast, the trans D10, octadecenoate isomer was almost excluded from liver phosphatidylcholines and phosphatidylethanolamines. Hepatoma phosphatidylcholines and phosphatidylethanolamines did not exhibit the degree of trans, D10, octadecenoate exclusion shown by liver. These data demonstrate the preferential incorporation of dietary geometrical isomers in specific lipid classes of liver, but not in hepatoma. The data also show the exclusion of some positional isomers from some lipid classes of liver and the loss of this specificity in some lipid classes of hepatoma.

161. EFFECT OF CYCLOPROPENE FATTY ACIDS ON THE DISTRIBUTION OF ISOMERIC OCTADECENOATES IN INDIVIDUALS LIPID CLASSES OF LIVER AND HEPATOMA.

Wiegand RD, Chumbler F, Wood R
Univ. of Missouri Sch. of Medicine, Columbia, MO 65201
J Am Oil Chem Soc; 53(2):149A 1976

Groups of normal and hepatoma (7288CTC) bearing rats were maintained on fat free diet containing 0.5% Sterculia foetida oil (SFO) for 4 weeks. The fatty acid composition of steryl esters, triglycerides, phosphatidylcholines, and phosphatidylethanolamines derived from normal livers, livers of animals bearing hepatoma (host), and hepatoma was determined. Also the octadecenoate fraction was isolated from steryl esters, triglycerides, phosphatidylcholines, and phosphatidylethanolamines of each hepatic tissue and the positional isomeric composition determined quantitatively. These data were compared with earlier studies using similar groups of rats fed fat free diet as controls. Sterculia foetida oil affects the fatty acid composition of the individual lipid classes of both the neutral lipid and phospholipid fraction differently. The fatty acid composition of both triglycerides and steryl esters of normal and host liver showed a dramatic reduction in the level of 18:1 and an increase in the percentage of 16:0 and 18:0 compared to the controls. The 18:0 level in the phospholipid fraction, in contrast to that in the neutral lipid fraction, was lower in normal and host liver phosphatidylcholines and phosphatidylethanolamines, and the 18:1 level was unaffected relative to the fat free diet controls. Hepatoma neutral lipid fatty acid composition was only marginally affected by Sterculia foetida oil, but the hepatoma phospholipid fraction showed a decrease in the percentage of 18:0 and an elevation of the 20:4 and 22:6 fatty acid percentages. Examination of the positional isomers of the liver octadecenoate fraction revealed an overall reduction in the level of vaccenic acid relative to the fat free diet controls. The characteristic 18:1 isomeric composition of each lipid class apparent in liver of non-hepatoma bearing rats consuming fat free diet was absent in those lipid classes isolated from the liver of rats consuming Sterculia foetida oil diet. In the four hepatoma lipid classes examined, all exhibited the same approximate proportion of oleic acid (70%) and vaccenic acid (30%) similar to that observed in hepatoma from rats consuming fat free diet.

162. EFFECT OF ESSENTIAL FATTY ACID DEFICIENCY ON THE LIPID COMPOSITION OF THE YOSHIDA ASCITES HEPATOMA (AH 130) AND OF THE LIVER AND BLOOD PLASMA FROM HOST AND NORMAL RATS.

Ruggieri S, Fallani A, Tombaccini D
Institute of General Pathology, University of Florence, Florence, Italy
J Lipid Res; 17(5):456-466 1976

In order to study the response of a poorly differentiated tumor to nutritional manipulation, the Yoshida ascites hepatoma (AH 130) was grown in rats fed an essential fatty acid (EFA)-deficient diet and in rats fed a control diet. Hepatomas, livers, and blood plasma from host rats and normal rats were studied as to the effects of EFA deficiency on the lipid composition. Normal rats fed an EFA-deficient diet showed an increased concentration of triglycerides and

cholesteryl esters in the liver and a reduced level of total phospholipids in plasma. Host rats fed the EFA-deficient diet showed a lower concentration of triglycerides in the liver when compared with the host rats fed a control diet. In addition, EFA-deficient host rats had reduced levels of plasma free fatty acids and triglycerides. These latter were markedly high in host rats under normal dietetic conditions. As compared to the livers of either host rats or normal rats fed the control diet, the Yoshida hepatoma cells had a lower content of total phospholipids and free fatty acids as well as a higher level of free cholesterol; they also showed a typical fatty acid pattern in their phospholipids. The main characteristics of this pattern were a high content of oleic and palmitoleic acids and a low level of C20 and C22 polyunsaturated fatty acids. Exposure of Yoshida hepatoma cells to an EFA-deficient environment resulted in a decrease in the concentration of total phospholipids and free fatty acids and in changes in the fatty acid composition similar to those observed in the livers of normal and host rats. These changes suggest that, under the experimental conditions used, the Yoshida hepatoma cells are responsive to EFA deficiency. (Author Abstract)

163. THE FATTY ACID COMPOSITION OF THE STEROL-WAX ESTER AND MONO- AND DIGLYCERIDE FRACTIONS OF MOUSE EPIDERMIS UNDERGOING NORMAL AND ABNORMAL GROWTH CHANGES.

Carruthers C, Heining A
Roswell Park Mem. Inst., Buffalo, N. Y.
Cancer Res; 24(6):1008-1011 1964

Sterol-wax ester, mono- and diglyceride fractions were determined from the total lipid fraction of normal Swiss mice epidermis 4, 12 and 22 days following plucking of hair from methylcholanthrene -treated epidermis (topical painting on alternate days for 6-8 wk) and carcinogen-induced squamous cell carcinomas. The sterol-wax ester fraction of the carcinomas differed from the normal or hyperplastic epidermis (which were essentially the same), in that it contained more palmitic, stearic and linoleic acid and less arachidic, methyl 11-eicosanoic, heneicosanoic, isobehenic, behenic and erucic acids. Arachidonic acid represented 12% of the carcinoma fraction whereas it was low or absent in the other two types. The mono-and diglyceride fraction from the carcinomas contained more stearic acid than the other two types. In this fraction a sexual difference was noted: following plucking, a female epidermis had a low level of lignoceric acid.

164. HORMONAL INFLUENCE ON FATTY ACID COMPOSITION OF STEROL ESTER AND PHOSPHOLIPID FRACTIONS OF EXPERIMENTAL MAMMARY CARCINOMAS (MEETING ABSTRACT).

Rees ED, Shuck AE, Ackermann H
U. Kentucky Med. Ctr., Lexington
Proc Soc Exp Biol Med; 128(3):666-670 1968

The fatty acid composition of the sterol ester (SE) and phospholipid (PL) fractions of mammary carcinomas induced in rats by 3-methylcholanthrene (MC) or 7,12-dimethylbenzanthracene, differed from those of the transplantable TC sarcoma (derived from a MC-induced mammary carcinoma, cultured in monolayer for 15 mo before sc inocn). Hormonal modification by oophorectomy followed by treatment with estradiol (50 MUg/d im), with or without progesterone (4 mg/d im), had no effect on the fatty acid composition of the PL fraction of the mammary carcinomas, except in those carcinomas which became fat-laden. In the fat-laden tumors, the PL and SE fractions showed increased proportions of shorter chain (C10-14) fatty acids and decreased proportions of polyunsaturated fatty acids (by comparison to nonfat-laden tumors). Differences in triglyceride composition were also noted. The hormone treatment increased lipid deposition in about 10% of the animals.

165. CHANGES IN (NA1 1 K1)-ATPASE ACTIVITY OF EHRLICH ASCITES TUMOR CELLS PRODUCED BY ALTERATION OF MEMBRANE FATTY ACID COMPOSITION.

Solomonson LP, Liepkalns VA, Spector AA
Dept. Biochemistry and Medicine, Univ. Iowa, Iowa City, IA 52242
Biochemistry (NY); 15(4):892-897 1976

The fatty acid composition of plasma membrane derived from Ehrlich ascites tumor cells was altered in vivo by changing the dietary lipid of the tumor-bearing mice. The activity of (sodium 1 potassium)-adenosinetriphosphatase ((Na1 1 K1)-ATPase), in partially purified plasma membranes, was measured as a function of temperature and fatty acid composition. Striking differences, dependent on membrane composition, were observed in the transition temperatures and in the energies of activation below the transition temperature. The transition temperatures for the (Na1 1 K1)-ATPase of plasma membrane derived from tumor cells grown in mice fed a regular chow diet containing a mixture of fatty acids (PMc), a 16% sunflower oil diet (PMSU), or a 4% tristearin diet (PMTS) were 20, 21, and 13.5 C, respectively. Energies of activation above the transition temperature were about the same (approximately 20 kcal/mol) in all three cases while the energy of activation below the transition temperature was about twice as high for the (Na1 1 K1)-ATPase of PMTS (approximately 60 kcal/mol) as for the (Na1 1 K1)-ATPase of either PMSU or PMC (approximately 30 kcal/mol). There were no significant differences in the cholesterol or phospholipid content in the three types of plasma membranes. There were however, marked differences in the fatty acyl composition of PMTS as compared with either the control (PMC) or PMSU membranes. The content of oleate (18:1 omega 9) and eicosatrienoate (20:3 omega 9) was higher and that of linoleate (18:2 omega 6) and arachidonate (20:4 omega 6) lower in PMTS than in PMc or PMSU. It is concluded that dietary lipid induced changes in membrane fatty acyl composition can change the activity of the plasma membrane (Na1 1 K1)-ATPase.

166. MODIFICATION OF THE FATTY ACID COMPOSITION OF EHRLICH ASCITES TUMOR CELL PLASMA MEMBRANES.

Awad AB, Spector AA
Dept. Biochemistry and Medicine, Univ. Iowa, Iowa City, IA 52242
Biochim Biophys Acta; 426(4):723-731 1976

The fatty acyl composition of Ehrlich ascites tumor cell plasma membrane structure was investigated by feeding the tumor bearing male CBA mice diets rich in either coconut or sunflower oil. With coconut oil, the oleate content of the membrane phospholipids was elevated while the linoleate content reduced. The opposite occurred with sunflower oil. Qualitatively similar changes were observed in the plasma membrane phosphatidylethanolamine, phosphatidylcholine and mixed phosphatidylserine plus phosphatidylinositol fractions. These diets also produced differences in the sphingomyelin fraction, particularly in the palmitic and nervonic acid contents. Unexpectedly, the saturated fatty acid content of the plasma membrane phospholipids was somewhat greater when the highly polyunsaturated sunflower oil was fed. The small quantities of neutral lipids contained in the plasma membrane exhibited changes in acyl group composition similar to those observed in the phospholipids. These fatty acyl group changes were not accompanied by any alteration in the

cholesterol or phospholipid contents of the plasma membrane. These results indicate that the fatty acyl group content of these cells can be changed by the dietary lipid content of the host and that the alterations are confined to the plasma membrane.

167. MODIFICATION OF THE FATTY ACID COMPOSITION OF MURINE LEUKEMIA CELLS (MEETING ABSTRACT).

Burns CP, Luttenegger DG, Wei SL, Spector AA
Univ of IA Coll of Medicine, Iowa City, IA. 52242.
Proc Am Assoc Cancer Res; 18:152 1977

The lipid requirements of the L1210 leukemia are supplied to a large extent by fatty acids taken up from the ascites fluid. We have compared the effect of diets containing 16% sunflower oil (polyunsaturated fat-rich) or 16% coconut oil (saturated fat-rich) fed for 0-7 weeks on the composition of tumor cell lipids. The L1210 phospholipids of mice eating the sunflower oil diet contained 14% monoenoic fatty acids as compared to 34% in the coconut oil group. In contrast, the sunflower oil group had 43% polyenoic fatty acids as compared to only 24% in the coconut oil group. The most prominent differences occurred in the proportion of oleate and linoleate. There was no difference in the percentage of saturated fatty acid. The degree of fatty acid unsaturation was greater for the sunflower oil diet (1.38 vs. 1.16 double bonds) and the average chain length also was longer (18.2 vs. 17.7 carbons). The majority of the changes occurred after 5 weeks of diet. The cellular cholesterol/phospholipid ratio was similar for the two groups. These results indicate that the fatty acid saturation of tumor cell phospholipids can be altered appreciably. Since most cell phospholipids are in membranes, our results suggest that it may be possible to alter the physical properties and functions of a tumor cell membrane by modifying the lipid composition of the diet. (Author Abstract)

168. LOCAL CHANGES IN CONTROL OF GROWTH DURING MAMMARY TUMORIGENESIS (MEETING ABSTRACT).

Hosick HL
Dept. Zoology, Washington State Univ,, Pullman, WA 99163
J Cell Biol; 70(2/Part2):170a 1976

Growth of mammary tumor cells of the mouse is not coordinated by the surrounding matrix of adipose tissue, as is growth of the normal mammary epithelium. It is likely, however, that the fatty stroma provides lipids which are metabolized by both normal and neoplastic epithelium. We are using cell-culture techniques to compare in detail the integrated responses of the normal and neoplastic epithelial cells to this local, and also to systemic, regulatory stimuli. Normal glands (of midpregnant C3H mice) are disassembled to individual cells by sequential collagenase-pronase treatments. Spontaneous mammary tumors are dissociated by gentle trypsinization. The resulting cells are seeded (separately) at 5×10^4 /cm^2 substrate area, and maintained in a nutrient medium containing 10% fetal calf serum and 5 ug/ml insulin (if either of these additives is deleted, both normal and tumor cells die). Growth is assessed by measuring the DNA accumulated in monolayers (in addition, the numerous viable cells sloughed spontaneously from postconfluent cultures are accounted for). When normal cells are supported with delipidated serum, less DNA accumulates than under the standard conditions. Conversely, when medium is supplemented with lipids (phosphatidyl choline, oleic acid), total DNA accumulated doubles within 3 days. This stimulatory effect is manifested only if the culture fluid contains one of several different steroid hormones. The tumor cells respond differently to this regimen: their utilization of exogenous lipids is not so finely adjusted by hormones. Conclusions: normal mammary epithelial cells in monolayer cultures retain their sensitivities to the dominant growth signals encountered in vivo (ie, the local lipid environment, and the hormones of pregnancy). Tumor cells in culture (and presumably in vivo) have partially lost their sensitivity to these controls.

F. Studies with Lipid Peroxides

169. MUTAGENICITY OF MALONALDEHYDE, A DECOMPOSITION PRODUCT OF PEROXIDIZED POLYUNSATURATED FATTY ACIDS.

Mukai FH, Goldstein BD
New York Univ. Medical Center, N.Y. 10016
Science; 191(4229):868-869 1976

A microbial mutagenesis assay system was used to investigate the mutagenicity of malonaldehyde, a lipid decomposition product. Twelve strains of Salmonella typhimurium were used: hisG46; TA1975; TA1535; hisC207; TA1976; TA1536; hisC3076; TA1977; TA1537; hisD3052; TA1978; and TA1538. Mutagenic activity was determined by standard spot tests and quantitative soft agar techniques. Malonaldehyde was prepared from malonaldehyde bis-(dimethylacetal). The results showed that malonaldehyde is mutagenically active, but only on frameshift mutants with normal excision repair (hisD3052 is the most sensitive). None of the base-pair substitution mutants tested showed any increase in revertant frequency. The pattern of mutagenic specificity was similar to that of Mitomycin C; both substances are DNA cross-linking agents. Malonaldehyde is especially prone to react with guanine and cytidine; the frameshift revertants of the hisD3052 mutation seem to be expressed as a result of guanidine-cytidine base-pairs. The relationship between these findings and human carcinogenesis or mutagenesis associated with lipid peroxidation or the ingestion of a diet high in polyunsaturated fatty acids remains conjectural; the observation of chromosomal aberrations in the circulating lymphocytes of man and Chinese hamsters following inhalation of low levels of ozone may be relevant because it is unlikely that ozone (which produces lung lipid peroxidation) can itself reach directly into the nucleus of circulating lymphocytes.

170. CARCINOGENS IN FOODS AND FOOD PRODUCTS. (PP. 67-73)

Sugimura T
Natl. Cancer Center Research Inst., Tokyo, Japan
Proceedings of the Eleventh Canadian Cancer Research Conference. Natl Cancer Inst Canada Toronto Ontario 6-8 May 1976, 1976.

Human beings are exposed to many carcinogens in foods. They may occur naturally in food sources, i.e., cycasin in cycad nuts and the active carcinogenic principle in bracken fern (a Japanese delicacy), or they may be naturally produced substances such as mycotoxins, which can contaminate food sources. Artificially introduced food additives may also be carcinogenic, such as the food preservative 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide, or they may interact with naturally occurring substances to produce carcinogens, as when nitrite reacts with secondary amines to yield nitrosamines. Many substances in food may influence the formation of these nitrosamines: gallic acid (related to tannin) and 4-methylcatechol (related to chlorogenic acid in coffee beans) enhance, whereas ascorbic acid, ubiquitous in fruits, depresses nitrosamine formation. The carcinogenicity of fatty acid peroxides in food has also been claimed; antioxidants, such as a-tocopherol, may prevent this formation. Nutritional status may also influence carcinogenesis in humans: e.g., vitamin B2 deficiency and hepatic injury resulting from inadequate food intake may promote hepatocarcinogenesis, and large quantities of salt, which by itself can produce stomach ulcers in experimental animals, may enhance the action of

gastrocarcinogens such as N-methyl-N'-nitro-N-nitrosoguanidine.

171. LIPID HYDROPEROXIDE ACTIVATION OF N-HYDROXY-N-ACETYLAMINOFLUORENE VIA A FREE RADICAL ROUTE.

Floyd RA, Soong LM, Walker RN, Stuart M
Biomembrane Res. Lab., Oklahoma Medical Res. Foundation, 825 Northeast 13 St., Oklahoma City, OK 73104
Cancer Res ; 36(8):2761-2767 1976

Linoleic acid hydroperoxide in the presence of methemoglobin or hematin activated the carcinogen N-hydroxy-N-acetyl-2-amino-flourene via the nitroxyl free-radical intermediate into 2-nitrosofluorene and N-acetoxy-N-acetyl-2aminofluorene. Ascorbate inhibited the activation, in which case the free-radical intermediate was replaced by the ascorbate free radical. Optical kinetics showed that the rate of linoleic acid hydroperoxide decrease paralleled the rate of N-hydroxy-N-acetyl-2-aminofluorene decrease and the rate of 2-nitrosofluorene increase. The stoichiometry of the reaction was such that, for every two linoleic acid hydroperoxide molecules consumed, two N-hydroxy-N-acetyl-2-aminofluorene molecules were oxidized and one 2-nitrosofluorene and one N-acetoxy-N-acetyl-2-aminofluorene molecule were formed. (21 refs)

172. CHEMICAL CARCINOGEN AND LIPOPEROXIDATIVE EFFECTS ON THE RIBOSOME MEMBRANE COMPLEX OF ROUGH MICROSOMAL MEMBRANES (MEETING ABSTRACT).

Shires TK
The Toxicology Center, Depts of Pathology and Pharmacology, The Univ of Iowa, Iowa City, IA 52242
Fed Proc; 36(3):1078 1977

Chemical carcinogens like dimethylnitrosamine (DMNA) and aflatoxin b (AFTX) cause an in vivo decline in the amount of rough endoplasmic reticulum in hepatocytes. From various studies both in vivo and in vitro, it has been deduced that carcinogens promote detachment of ribosomes from the rough membranes (Rmic). We have isolated Rmic from rat liver, incubated it with either DMNA or AFTX and by density gradient centrifugation assayed for ribosomal detachment. Using incubation systems that demonstrably supported metabolism of carcinogen or amino acid incorporation in the presence of carcinogen, no evidence for ribosomal detachment was found, nor was there detachment after concurrent metabolism and incorporation. However, if lipoperoxidation was allowed to occur in the metabolizing system by adding increased amounts of NADPH (1 mM) giving 15-20 nmoles malondialdehyde /mg, ribosomes appeared to detach but, in so doing, carried much Rmic phospholipid with them. If lipoperoxidation was restrained with antioxidant no detachment occurred unless K**+ concentration was elevated to 750 mM. The presence of carcinogen was not required for lipoperoxidation, the NADPH was alone a sufficient pro-oxidant. While even minimal lipoperoxidation alters the domain of the binding site, detachment does not seem a likely explanation for carcinogen-promoted decline in the extent of liver rough membranes in vivo. (Author Abstract)

173. SPIN TRAPPING AND ITS APPLICATION IN THE STUDY OF LIPID PEROXIDATION AND FREE RADICAL PRODUCTION WITH LIVER MICROSOMES.

Saprin AN, Piette LH
Dept. Kinetics of Chemical and Biochemical Processes, Inst. Chemical Physics, Acad. Sciences, Moscow, USSR
Arch Biochem Biophys; 180(2):480-492 1977

Electron spin resonance was used to detect free radical adducts of phenyltertiarybutylnitrone produced during induced lipid peroxidation of microsomes with a system consisting of NADPH, Fe^{2}+, and pyrophosphate. The adducts were identified as intermediates of the substrates added to the microsomal system rather than as OH. or HO2. radicals. The production of the adduct was parallel to the NADPH-dependent formation of malondialdehyde. Analyses of the electron spin resonance hyperfine splitting constants allowed identification of the adducts in some instances. Purified preparations of cytochrome P-450 mimicked the results of the microsomes. When the carcinogens dimethyl- and diethylnitrosoamine were metabolized in this system, reactive free radicals and free NO were produced, suggesting an alternate mechanism for the activity of these compounds as ultimate carcinogens. (30 Refs)

174. PEROXIDATED LIPID CONTENT OF HUMAN BREAST FLUID.

Petrakis NL, Doherty MA, Lee RE, Beelen G
G. W. Hooper Foundation, University of California, San Francisco, California 94143
Proc Am Assoc Cancer Res; 16:157 1975

Lipid peroxidation, in vivo, has been reported to be a source of free radicals which may be destructive to cell membranes, enzymes and other cellular components, and possibly to have carcinogenic potential. The extent of lipid peroxidation in breast secretions was investigated in nipple aspirates from 95 women, ages 20 to 70 years, who were clinically diagnosed as having normal breasts, cystic disease, or carcinoma. Duct secretions were aspirated with a modified breast pump and the concentration of peroxidated lipids was determined by the fluorescence technique of Tappel. The values obtained ranged from 0 to 400 fluorescence units. A progressive but moderate increase in concentration of peroxidated lipids was found with age in fluid from normal breasts. Significantly elevated levels of peroxidated lipids were present in fluid from cystic disease, whereas cancerous breasts showed wide variations in concentration. Studies are in progress on the GSH peroxidase activity of breast fluid and of the possible effect of dietary alteration on the concentration of peroxidated lipids in breast fluid. The findings may have relevance to current epidemiologic studies which suggest an etiologic role of dietary fat in breast cancer. (Author Abstract)

175. GSH-PEROXIDASE ACTIVITY OF HUMAN BREAST TISSUE (MEETING ABSTRACT).

Petrakis NL, Doherty M, Lee R, Mason L
Hooper Foundation, University of California, School of Medicine, San Francisco, Ca. 94143
Proc Am Assoc Cancer Res; 17:138 1976

Lipid peroxidation, in vivo, produces free radicals that may damage intracellular membranes and enzymes and may have carcinogenic activity. We found that with advancing age, nipple aspirates of breast fluid contain increasing amounts of peroxidated lipids, with highest levels in breast cancer patients. The enzyme GSH-peroxidase metabolizes lipid peroxides, preventing accumulation of toxic conjugated dienes, malonaldehyde and fluorescent products. We have measured the activity of GSH-peroxidase in breast tissue by the assay of Chow, Reddy and Tappel (J Nutr 103:618, 1973). GSH-peroxidase activity was expressed as n mols of NADH oxidized/min/mg protein in breast tissue from 29 women undergoing biopsy for a breast mass or reduction mammoplasty, compared with GSH-peroxidase activity assayed on red blood cells from normal women. Human breast tissue had a significantly lower activity of GSH-peroxidase than erythrocytes (x equals 131.4 plus or minus 20.4 n mol versus 210.3 plus or minus 14 n mol) with most values for breast

under 75 n mol. These findings suggest breast tissue may have a limited capacity to metabolize peroxidated lipids whose accumulation may enhance carcinogenicity of other substances. The findings are relevant to epidemiologic studies, indicating an etiologic role for dietary fat in human breast cancer. (Author Abstract)

G. Biochemical and Other Studies Concerning Lipids

176. THE EFFECT OF DIETARY LIPIDS ON 3,4,BENZO(A)PYRENE METABOLISM IN THE HEPATIC ENDOPLASMIC RETICULUM.

Lambert L, Wills ED

Dept. Biochemistry, Medical Coll. St. Bartholomew's Hosp., Charterhouse Square, London, E.C.1M 6BQ, England

Biochem Pharmacol; 26(15):1423-1427 1977

The effect of variations of the nature of the lipid content of the diet has been studied on the rate of formation of hydroxylated derivatives of benzoapyrene in liver endoplasmic reticulum. Measurements were made by a fluorimetric determination of the hydroxylated products and by separation of radioactive products from labeled benzoapyrene. Hydroxylation was minimal when a fat free diet was fed, little affected by addition of 10% lard (containing mainly saturated and monounsaturated fatty acids but only 6% linoleic acid) but increased to a significant extent by 10% corn oil (containing 50% linoleic acid). Addition of 10% herring oil (containing 15.4% polyunsaturated fatty acids but only 1.7% linoleic acid) to the diet did not increase the rate of hydroxylation. Methyl linoleate significantly increased the rate of hydroxylation, Vitamin E did not affect it and cholesterol was inhibitory by some tests. These experiments demonstrate similarities and important differences in the responses of oxidative demethylation of drugs and hydroxylation of carcinogens to dietary lipids. Both processes are enhanced by a supply of dietary linoleic acid but cholesterol and Vitamin E which stimulate oxidative demethylation do not significantly affect hydroxylation of benzoapyrene. These different requirements for dietary lipids may demonstrate that membranes of different structure are required for max activity of the two enzyme systems. (Author abstract) (17 Refs)

177. THE EFFECT OF CYCLOPROPENOID FATTY ACIDS ON BINDING OF AFLATOXIN B1 TO NUCLEAR DNA, RNA AND PROTEIN OF RAT HEPATOCYTES.

Scarpelli DG, Rao MS, Reddy JK

University of Kansas Medical Center, Kansas City, Ks 66103

Proc Am Assoc Cancer Res; 16:164 1975

C18 and C19 fatty acids containing a cyclopropene ring (CPFA's) natural compounds in plants of the order Malvales have been shown to augment the carcinogenic effects of aflatoxin B1 (AFB1) and recently identified as a potent mitogen for hepatocytes. Experiments to ascertain whether CPFA's affect the binding of AFB1 to DNA, RNA and protein of rat liver cells were carried out. 50 gm male Sprague-Dawley rats were fed a synthetic diet containing 500 ppm of CPFA's supplied as triglycerides in Sterculia foetida oil ad libitum for 2 wks. Comparable animals fed synthetic diet alone served as controls. Animals were injected IP (3.microC/100 gm B.W.) with C^{14} ring labeled chromatographically pure AFB1 (Sp. Ac. 5.37.microC/microM) dissolved in N-methylformamide and sacrificed 1 hr later. DNA, RNA and protein were extracted; DNA was further purified by treatment with pronase, RNA-ase, and by density gradient centrifugation on CsCl2. These results corroborate earlier work (Lijinsky, W., Lee, Y.L., and Gallagher CH, Cancer Res: 30:2280, 1970) that AFB1 binds to a greater degree to protein and RNA than to DNA. Ingestion of CPFA enhanced binding of AFB1 to protein by 39.9%, RNA 35.5% and DNA 37%. This effect of CPFA may be related to its potentiation of AFB1 induced hepatocarcinoma. (Author Abstract)

178. THE DISTURBANCE OF OXIDATIVE PHOSPORYLATION BY THE CARCINOGENS 12-HYDROXYSTEARIC ACID AND ITS METHYL ESTER (MEETING ABSTRACT). (P. 192)

Hadler HI, Mueller KW

Dept Chem and Biochem, So IL Univ, Cabondale, IL 62901

Third International Symposium On Detection And Prevention Of Cancer. 1976.

In a search to determine common molecular features in potential carcinogenic dietary fatty acids Swern et al, (Cancer Research 30, 1037-1046, 1970) found that 12-hydroxystearic acid and its methyl ester were carcinogenic. This was surprising to Swern et al, and Shimkin et al, (Cancer Research 32, 880-881, 1972) as it was not readily apparent how the above two agents could be converted to alkylating agents. We have observed that the carcinogens 12-hydroxystearic acid and its methyl ester disrupted oxidative phosphorylation in rat liver mitochondria. The in vitro mitochondrial effects induced by the agents included: a) uncoupled respiration, b) ATPase activity, c) energized volume changes linked either to respiration or ATP. Mitochondria mediated the enzymic conversion of the ester to the acid. Conversion was retarded by the thiol reagent showdomycin. These data in conjunction with previous reports contribute to an experimental confluence between oxidative phosphorylation and chemical carcinogenesis and draw attention to our unitary hypothesis for carcinogenesis which implicates oncogenic properties for nucleic acid released from damaged mitochondria. (Author Abstract)

179. LIPID METABOLISM IN CULTURED CELLS: GROWTH OF TUMOR CELLS DEFICIENT IN ESSENTIAL FATTY ACIDS.

Bailey JM, Dunbar LM

George Washington U. Sch. Med., Washington, D.C.

Cancer Res; 31(2):91-97 1971

Growth of Ehrlich ascites carcinoma and sarcoma 180 were studied in normal DF1 mice and CF1 mice with pronounced essential fatty acid deficiency through periodic assay of the fatty acid composition in whole blood. Mice fed a fat-free diet grew more slowly than controls during the first 5 wk at which time they ceased growing, while control mice continued to gain weight for a further 4-6 wk. The sharpest decline in blood linoleic acid occurred during the first month in the deprived animals with a drop in blood lipids from 17.5% to less than 5% of the total fatty acid; at 6 months blood lipids decreased to 0.5% or less than 1/30 of the normal amount. Growth of tumors from cells harvested from Ehrlich ascites carcinoma showed a similar pattern in normal and deficient mice with a somewhat longer lag phase following inoculation. Similarly, cells harvested from a sarcoma 180 showed a somewhat longer lag period after inoculation into the deficient mice, but mean generation times measured over the entire growth curve were not significantly different. The total lipid content of the Ehrlich ascites tumor of the deficient mice (0.76 0.13 mg lipid/107 cells) was (0.67 0.12 mg/107 cells) despite decreases in linoleic acid and arachidonic acid due to simultaneous increases in palmitoleic acid, oleic acid,and eicosatrienoic acid. Increase in dividing time occurred in the initial stages of growth when both Ehrlich ascites and normal sarcoma 180 cells were transplanted into deficient mice, but

growth rate returned to normal after the first 24-48 hr. This fact and the apparently normal transplantation characteristics of the deficient cells in both normal and deficient hosts suggests that the deficient environment did not represent any major metabolic stress.

180. TRANSPORT CHANGES ASSOCIATED WITH GROWTH CONTROL AND MALIGNANT TRANSFORMATION.

Weber MJ, Hale AH, Yau TM, Buckman T, Johnson M, Brady TM, La Rossa DD
Dept. Microbiology, Univ. Illinois, Urbana, IL 61801
J Cell Physiol; 89(4):711-722 1976

The rate of uptake of nutrients and ions in chick embryo fibroblasts that were either density-inhibited, growing exponentially, or transformed by Rous sarcoma virus was determined. When normal growing cells were compared to transformed cells, only one change was detected: uptake of 2-deoxyglucose and 3-O-methylglucose was increased three- to fivefold in the transformed cells. ^{3}H-ouabain binding showed that there were fewer ouabain binding sites on the density-inhibited cells than on the growing cells. The uptake of ^{3}H-2-deoxyglucose was measured at temperatures from 43 to 0 C, and the data were utilized to construct Arrhenius plots. The slope of the plot was steeper for the transformed cultures than for the normal cultures. To examine the time course of appearance of the tumor virus-induced fatty acid alterations, the temperature-conditional mutant of Rous sarcoma virus (RSV-T5) was used. Chick cells infected with RSV-T5 and held at 36 C had a transformed phenotype and had a fatty acid composition typical of transformed cells, but the culture held at 41 C had a normal phenotype and a normal-type fatty acid composition. At time zero, cultures were shifted to the opposite temperature. At 10 and 26 hr after the shift, cultures were taken for analyses. Although the switch in the capacity to take up 2-deoxyglucose was complete within 26 hr, the changes in fatty acid composition were less than half complete. The addition of proteases (including plasmin) to normal, density-inhibited cultures did not stimulate them to take up 2-deoxyglucose at a rate much above that characteristic of normal, growing cells. Addition of dibutyryl cyclic AMP to cells transformed by RSV-T5 restored the transformed level of 2-deoxyglucose uptake to normal. The results indicate that there are two classes of transport control in cultured chick cells. (50 Refs)

SUBJECT INDEX

Age, 22, 23, 30-33, 36-38, 49, 53, 58, 155, 174, 175
Alkaloids, 79, 87, 154
Amino Acids, 146
Antioxidants, 172
  ascorbate, 24, 63, 72, 170, 171
  BHA, 93
  BHT, 93, 143
  tocopherol, 64, 78, 151, 170, 176
Bacteria (see Gut Microflora)
Bile Acids, 2, 6, 8, 11, 14, 17, 20, 21, 34, 56, 63, 67, 69, 72, 73, 77, 114-116, 118, 119, 148
  deoxycholic, 1, 12, 13, 15, 16, 115
  lithocholic, 1, 12, 13, 15, 16, 118
  metabolites, 7, 15
  taurodeoxycholic, 118
Biomagnification, 89
Blood Group (see Genetic Factors)
Calories, 24, 50, 54, 57, 59, 65, 68, 70
Cancer (see Neoplasia)
Candicidin, 114
Carbohydrates, 24, 32, 63, 64, 104, 139, 157, 158
Carcinogens
  acetylaminofluorene, 124, 137, 145, 171
  asbestos, 69
  azoxymethane, 15, 114, 115
  cycasin, 79, 170
  cyclopentophenanthrene, 6
  dimethylaminoasobenzene, 157, 158
  dimethylbenzanthracene, 51, 112, 113, 125-128, 130, 131, 143
  dimethylhydrazine, 15, 116-122, 147, 150
  ethionine, 149
  fluorenylacetamide, 149, 159
  halogenated hydrocarbons, 69
  20-methylcholanthrene, 123, 140, 146, 163
  mycotoxins, 69, 79, 80-84, 90, 134-139, 149, 151-153, 170, 172, 177
  nitrosamines, 59, 63, 69, 90, 95, 96, 116, 117, 122, 129, 134, 149, 170, 172, 173
  polycyclic aromatic hydrocarbons, 17, 48, 73, 85, 93, 94, 99, 101-103, 176
  urethane, 59
Cholesterol, 1, 3, 7, 12, 34, 47, 54, 55, 61, 72, 73, 76, 77, 100, 107, 108, 115, 117, 118, 123, 135, 159, 166, 167, 176
  cholesteryl esters, 160, 162
  cholestyramine, 69, 114
Diet, 27, 29, 33, 50, 57
  fat-free, 158, 176, 179
  high-fat, 5, 15, 17, 25, 26, 28, 32, 34, 36, 51, 55, 58, 59, 64, 65, 68, 69, 72, 77, 104, 116, 118, 120, 128-133, 141, 146-149, 155
  low-fat, 34, 70, 116, 126, 129-131, 141, 157
  vegetarian, 1, 51, 66
  Western, 7, 13, 18, 34, 51, 56, 60, 73
Dietary Habits, 47, 56, 60, 66
Disease
  atherosclerosis, 5, 16, 75
  breast, 30, 174
  cirrhosis, 59, 60, 62, 81, 155
  diabetes, 38-40, 47
  diverticulitis, 5, 17
  glaucoma, 87
  heart, 9, 16, 19, 41, 55, 61, 63, 78, 87
  hypertensive, 38, 40
  multiple sclerosis, 62
  ulcerative colitis, 5, 17, 47
Environmental Factors, 3, 12, 16, 18, 25, 28, 30, 31, 33, 35, 36, 56, 57, 63, 68-70, 89, 90, 129
Enzymes
  aminopyrine demethylase, 122, 151
  ATPase, 165, 178
  benzpyrene hydroxylase, 73, 122, 145, 151, 176
  beta-glucuronidase, 12, 13, 77
  cytochrome P-450, 122, 173
  GSH peroxidase, 29, 174, 175
  mixed function oxidases, 57, 122
  p-nitroanisol demethylase, 145, 151
  sulfotransferase, 35
Familial Cancer, 32, 41, 47
Fats and Oils
  animal, 13, 14, 48, 49, 52, 56
  argemone, 86, 87
  butter, 94
  coconut, 127, 143, 166, 167
  corn, 99, 105-107, 117, 119, 120, 121, 126, 138, 142, 143, 176
  cottonseed, 79, 134, 142
  heated, 94, 97, 98-102, 124
  herring, 176
  lard, 70, 108, 120, 131, 176
  margarine, 102
  mustard, 86
  olive, 123
  orange, 85
  peanut, 84, 86
  polyunsaturated, 44, 45, 75, 127, 141, 143, 144
  safflower, 127
  salmon, 137, 138
  sassafras, 79, 85
  saturated, 7, 13, 19, 22, 45, 50, 55, 66, 135, 140, 142
  sesame, 137
  soybean, 86, 100
  Sterculia foetida, 134, 136, 137, 161, 177
  sunflower, 94, 98, 124, 141, 160, 165-167
  tallow, 115, 117, 119, 121, 141, 146
  unsaturated, 19, 76, 135, 139
  vegetable, 78, 99
Fatty Acids, 105, 180
  arachidonic, 142, 163, 165, 179
  behenic, 163
  cyclopropenoid, 79, 134, 136-138, 161, 177
  eicosanoic, 163
  eicosatrienoic, 165, 179
  erucic, 163
  free, 162
  glycidyl esters, 110

lignoceric, 163
linoleic, 44, 100, 106, 111, 127, 128, 140, 142, 143, 163, 165-167, 171, 176, 179
monenoic, 167
nervonic, 166
nitroperoxybenzoic, 110
oleic, 106, 111, 113, 125, 127, 161, 162, 165, 167, 168, 179
octadecanoic, 112, 113, 161
palmetoleic, 162, 179
palmitic, 163, 166
polyenoic, 167
polyunsaturated, 29, 78, 140, 162, 164, 169
saturated, 7, 52
stearic, 110, 128, 163, 178
stearohydroxiamic, 110
sterculic, 135
steryl esters, 161
unsaturated, 112
vaccenic, 161
Fecal Steroids (see Hormones)
Feces, 8, 11, 20, 34, 56, 114
Fertility, 39
Fiber, 5, 11, 14, 16-22, 56, 57, 67-69
Food
alcohol, 3, 14, 47, 55, 58, 60, 62, 63, 69, 73
bacon, 95, 96, 101
beef, 1, 7, 14, 22, 52, 66
bracken fern, 170
chocolate, 103
coffee and tea, 53, 58, 170
eggs, 58, 60, 108, 109
meat, 3, 7, 8, 16, 52, 58, 61, 66, 77, 101, 102, 119
milk, 3, 23, 58, 60, 69, 87
peanuts and seeds, 80, 81, 82, 84, 86
pork, 22
refined, 5, 20, 33, 58, 65, 67
vegetables and fruits, 3, 29, 58, 60, 63, 147, 170
Genetic Factors, 16, 21, 32, 33, 56, 74, 132
Geographic Factors, 1, 12-14, 17, 18, 22-24, 28, 31, 33, 34, 36, 39, 47, 49, 50, 57, 58, 60, 62, 65, 68, 70, 73, 76, 81, 84, 87
Germ-free Rats, 122
Glutathione, 29, 145
Griseofulvin, 79
Gut Microflora, 1-3, 12, 13, 15-17, 20, 27, 34, 56, 57, 59, 72, 73, 77, 115, 118, 122, 148, 150
bacteroides sp., 8
clostridia sp., 6, 8, 11
Hormones and Sterols, 40, 52, 57, 59, 70, 144, 168
androgens, 30, 35, 43, 132
androstenedione, 43, 72
coprostanol, 13
DES, 39
DHEAS, 35
estradiols, 34, 43, 50, 105, 164
estriols, 30
estrogens, 25, 27, 30, 32, 34, 35, 37-39, 41-43, 47, 69, 70, 72, 106, 130-132
estrones, 43, 50, 72
gonadotropins, 43
neutral sterols, 2, 6, 15, 16, 20, 21, 56, 77, 115, 116, 118, 119
oral contraceptives, 32
progesterones, 39, 164
prolactin, 25, 26, 28, 51, 63, 130-132
sterol esters, 164
testosterone, 43, 51
Immunological Factors, 32, 53, 57, 140, 144, 148
Ionizing Radiation, 30, 36, 49, 69
Life-style, 50, 66, 69
Lipids, 29, 83, 108, 109, 139, 179
diglycerides, 163
D-limonene, 85
gossypol, 138
lecithin, 107
3-methylcoumarin, 138
monoglycerides, 163
mono-olein, 107
monostearin, 107, 125
neutral, 161, 166
phospholipids, 159, 161, 162, 164, 166, 167
sphingomyelin, 159, 166
triglycerides, 135, 160-162, 164, 177
tristearin, 165
unsaturated, 60
Lipophilic Substances, 89
Lipoperoxidation, 143, 169, 172-175
Lipoprotein, 47
Lipotropes, 148, 149, 151-153 (see also Vitamins)
S-adenosylmethionine, 145, 146
choline, 60, 145-147, 150, 154-158
folate, 60, 145, 146
methionine, 60, 145-147, 150
Malonaldehyde, 169, 175
Membranes, 144, 159, 165-167, 172, 174, 175
Menarche, 30
Menopause, 30, 36, 38-43
postmenopausal, 25, 26, 31, 36, 39, 40, 42, 43
premenopausal, 25, 31, 36, 43, 51
Menstrual Cycle, 51
Metabolism, 2, 4, 20, 32, 56, 57, 59, 73, 144, 148, 156-158
bacterial, 12, 13, 57
lipid, 114, 172, 173, 175, 176, 179
steroid, 13, 67, 72
Molds, 83, 84
Morbidity, 17, 28
Mortality, 4, 17, 18, 20, 23, 24, 28, 29, 32, 36, 52, 58, 62, 65, 66, 76
Neoplasia
adenocarcinoma, 23, 39, 108, 116, 141, 142
ascites, 165, 166, 179
biliary, 47, 123
bladder, 58, 70, 87, 149
bowel, 4, 6-10, 12, 56, 62, 69
brain, 65, 106, 107
cervical, 31, 39, 55, 65, 70, 128
chromophobe adenoma, 104
colonic, 1, 2, 3, 5, 6, 11, 15-21, 31, 55, 56, 59, 60, 63, 64, 66-69, 72, 73, 77, 116-122, 147-150
colorectal, 13, 14, 19, 22, 52
duodenal, 10
ear duct, 150
endometrial, 16, 31, 37-43, 50, 55, 56, 65, 67, 70, 72
esophageal, 56-60, 64, 70, 72, 73, 87, 149
fibrosarcoma, 106
gastric, 23, 24, 56-58, 60, 63, 65, 67, 68, 70, 72, 82, 98, 106, 113, 124, 147
gastrointestinal, 24, 58, 65, 82, 99, 114
heart, 106
hepatic, 57-60, 65, 69, 79, 81, 84, 85, 92, 123, 124, 134-138, 146, 148, 149, 151-158, 160-162, 170
Hodgkin's, 53, 65, 70
ileal, 10
jejunal, 10
laryngeal, 58, 62, 63, 65, 73
leukemia, 49, 58, 59, 65, 133, 167
lymphoma, 46, 53, 112
lymphosarcoma, 65, 99, 106, 108, 109
mammary, 16-18, 25-36, 50-52, 55, 56, 58-60, 62-72, 108, 109, 126-132, 140, 142, 164, 168, 174, 175

melanoma, 44, 45, 49
multiple myeloma, 65
oronasopharyngeal, 58, 59, 62, 64, 65, 73, 87
ovarian, 31, 55, 58, 59, 65, 67
pancreatic, 18, 47, 55, 58, 65, 69
pituitary, 104
preneoplastic, 25, 71
prostatic, 16, 18, 48, 55, 58, 65, 69
pulmonary, 58, 65, 69, 70, 75, 92, 98, 106, 108, 109
rectal, 3, 17, 19, 58, 59, 62, 65, 73
renal, 18, 55, 65, 69, 82, 106, 134
rhadbomyosarcoma, 105, 106
salivary gland, 82, 124
skin, 45, 49, 65, 69, 85, 87, 98, 112, 113, 124, 125, 163
testicular, 65, 128
thyroid, 55, 65
vaginal, 39
Nitrates, 72
fertilizers, 48, 64
Nucleic Acids, 177, 178
cyclic nucleotides, 25, 180
Nutrition, 26, 28, 31, 40, 54, 55-57, 59, 61, 69, 139
nutritional deficiencies, 55-57, 59, 60, 63, 170
Obesity, 30-32, 35-43, 46, 47, 50, 53, 55, 56, 64, 72
Ovaries
oophorectomy, 30, 164
ovarian function, 28, 31, 39, 131
Parity, 22, 23, 36
Pollutants, 69, 88
aldrin, 88-90
chlordane, 89, 91
DDT, 89-91, 133
dieldrin, 88-91
endrin, 88
heptachlor, 88, 89
methylmercury, 90
organochlorines, 88-90
polychlorinated biphenyls, 90
Populations, 2, 6, 11, 12, 16, 18-21, 29, 33, 36, 47, 67
Polyps, 5
Pregnancy, 47, 154, 168
Promotion, 1, 12, 15, 63, 69, 73, 74, 85, 112, 114, 125, 126, 144
Protein, 10, 20, 57, 59, 71, 73, 90, 104, 117, 119, 135, 139, 147, 155, 157, 177
animal, 7, 9, 13, 18, 24, 52, 68, 77, 109, 121
vegetable, 121
Puberty, 26
Racial and Ethnic Factors
Black, 22, 47
Caucasian, 3, 12, 26, 47, 51
Japanese, 1, 3, 7, 12, 26, 31, 35, 51, 60, 70, 73
Seventh-Day Adventist, 21, 66
Other, 13, 21, 32, 40
Reserpine, 30, 36, 69
Safrole, 85
Salt, 69, 170
Sex, 22, 23, 47-49, 58, 69, 73, 81, 140, 155, 163
Socioeconomic Factors, 1, 3, 14, 17, 22, 36, 40, 47, 60, 61, 62, 68, 69
Tobacco, 3, 41, 47, 53, 55, 58, 60, 63, 69, 70, 73, 75
Transit Time (mouth-anus), 11, 16, 17, 21, 63
Trace Metals, 57, 71
iron, 70, 73
selenium, 29
Tryptophan, 52
Tumors
benign (see Polyps)
malignant (see Neoplasia)
Viruses, 30, 52, 60, 72, 132, 180
Vitamins, 57, 71, 139, 151 (see also Antioxidants and Lipotropes)
A, 24, 64, 72, 148
B complex, 24, 63, 72, 73, 146, 154, 170

BLANK PAGE

AUTHOR INDEX WITH CITATION NUMBERS

Abraham S 142
Ackermann H 164
Adams JB 35
Alcantara EN 57
Arffman E 111
Arffmann E.. 100, 112, 113
Asvall J 23
Awad AB 166
Ayres JL 137, 138
Bailey DM 143
Bailey JM 179
Bain GO 123
Barell V 67
Beelen G 174
Beniashvili DS 94
Berg JW 7
Berglund F 82
Berndt H 17
Bills DD 96
Bishop OS 65
Blitzer EC 37
Blitzer PH 37
Boger E 85
Boicchi M 92
Boschetti NV 106
Brady TM 180
Brown J 99
Buckman T 180
Burkitt DP 20
Burns CP 167
Campbell RL 114, 115
Cardeilhac PT 83
Carroll KK 71, 126
Carruthers C 163
Chan P 25, 51, 73
Chan PC 26, 129, 130, 131
Charles RT 92
Chechelashvili 94
Choi NW 27
Chumbler F 160, 161
Cohen L 25, 51
Cohen LA 26, 129, 130, 131
Cole P 50
Collins IS 91
Cramer D 50
Crawford WA 91
Cutler MG 128
Dales LG 22
Davis NC 44
Dayton S 75, 127
De Waard F 31, 40, 42
Dhar AK 77
Dodo H 3
Doherty M 175
Doherty MA 174
Drasar BS 8, 68
Dunbar LM 179
Dzagnidze LN 94
Eastcott DF 49
Ederer F 76
Egan H 90
Eppenberger U 72
Epstein SS 89
Estape J 32
Fabian B 102, 103
Falk HL 74
Fallani A 162
Floyd RA 171
Frantz ID 76
Fraumeni JF 47
Friedman GD 22
Gaines TB 133
Gantt JS 114
Gibson DD 143
Glaeser F 38
Glavind J 111, 112, 113
Goddard P 34
Goldrick RB 44
Goldstein BD 169
Goodwin RM 44
Gori GB 4
Gothoskar SV 86
Grantham PH 145
Gregor O 24
Grossman S 22
Gusberg SB 39
Hadler HI 178
Haenszel W 7
Hakim SA 87
Hale AH 180
Hamilton PB 139
Harr JR 134
Hashimoto S 127
Head JF 131
Hegsted DM 61
Heining A 163
Heinivaara O 104
Helberg D 93
Hems G 33
Heyden S 70
Hildrum KI 96
Hill MJ 6, 8, 11, 16, 34
Hill P 25, 26, 51, 64
Hoffmann D 73
Homburger F 85
Hopkins GJ 141, 144
Hosick HL 168
Howell MA 52
Hubbard AW 90
Hueper WC 99
Hunt R 140
Hutcheson DP 117
Hyde RT 53
International A 88
Irving D 68
Ishikawa S 3
Jacob A 157, 158
Johnson M 180
Judd HL 43
Kajitani T 3
Khor HT 126
Kim U 132
Kimbrough R 133
King MM 143
Kler HW 113
Knox EG 62
Kowalewski K 123
Krasnyanskaya P 94
Kummerow FA 159
Kuno K 51
Kurihara M 7
La Rossa DD 180
Lambert L 176
Landers MK 134
Langman MJ 9
Lee DJ ..134, 136, 137, 138
Lee R 175
Lee RE 174
Leffert H 156
Leren P 76
Levin ML 30
Libbey LM 96
Liepkalns VA 165
Lijinsky W 101
Lillenfeld AM 36
Lin YN 114, 115
Ling KH 84
Locke FB 7
Lowenfels AB 10
Lubin F 67
Luttenegger DG 167
Mackie BS 45
MacCornack F 26
MacLennan R 14
Marisawa R 119
Maronpot R 118
Martin CW 122
Mason L 175
Mastromarino A 2
Matthews VL 27
McCay PB 143
McDonough M 110
McIlMurray MB 9
Meranze DR 110
Mertin J 140
Meunier M 157
Miller AB 27, 28
Modan B 67
Modan M 67
Mueller KW 178
Mukai FH 169
Munan L 27
Nair KP 83
Nerisawa T .. 118, 120, 121
Nestel PJ 44
Newberne PM60, 147, 148, 150, 151, 152, 153, 154
Nigro ND 114, 115
Nixon JE 134
O'Gara RW 99
Paffenbarger RS 53
Palmblad J 46
Payet M 81
Peacock PB 69
Pearce ML 75
Perkins RG 159
Petrakis NL ..29, 174, 175
Phillips RL 66
Piette LH 173
Pitha JV 143
Poirier LA 145
Poyser A 44
Prusova F 24
Quinlivan NL 44
Ranadive KJ 86
Rao GA 142
Rao MS 177
Reddy B 73
Reddy BS1, 2, 12, 13, 15, 77, 116, 118, 119, 120, 121, 122
Reddy JK 177
Rees ED 164
Reuber MD 155
Rimm AA 37
Rogers AE60, 145, 146, 148, 149, 150, 151, 152, 153
Rotkin ID 48
Rowland IR 18
Ruggieri S 162
Ryan KJ 41
Saffiotti U 125
Saprin AN 173
Scanlan RA 96
Scarpelli DG 177
Schindler AE 38
Schneider R 128
Schrauzer GN 58
Segi M 7
Sheinfil A 119
Shennan DH 65
Sherman JD 133
Shils ME 59
Shimkin MB 110
Shires TK 172
Shubik P 101, 125
Shuck AE 164
Siegenberg J 123
Singh DV 114, 115
Sinnhuber RO134, 136, 137, 138
Solomonson LP 165
Sonni A 10
Soong LM 171
Speckmann EW 57
Spector AA .. 165, 166, 167
Stewart L 99
Stuart M 171
Sugimura T 170
Swern D 110
Szepsenwol J105, 106, 107, 108, 109
Takano A 3
Tezabwala BU 86
Thomas DB 30, 36
Thompson TF 5
Toman R 24
Tomatis L 92
Tombaccini D 162
Tung TC 84
Turkiya NB 94
Turpeinen O 76
Turusov V 92
Ury HK 22
Van der Linde F 56, 72

Van Veldhuizen.....80
Vartiainen I.....104
Vukusich D.....77, 120
Vysheslavova M.....98, 124
Wales JH.....136, 137, 138
Walker AR.....20, 21
Walker RN.....171
Weber MJ.....180
Wei SL.....167
Weisburger J.....64
Weisburger JH26, 77, 116, 118, 119, 120, 121, 122
Wells PA.....135
West CE.....141, 144
Wetterstrand WH.....19
Wieder R.....110
Wiegand RD.....160, 161
Williams RE.....8, 34
Williams SR.....22
Wills ED.....176
Wilson CS.....29
Wilson RB.....117
Wing AL.....53
Wogan GN.....79
Wollman J.....127
Wood R.....160, 161
Wynder E.....2, 51
Wynder EL1, 3, 12, 13, 25, 26, 54, 55, 63, 73, 77, 116, 118, 119, 120, 129, 131
Yau TM.....180
Zaldivar R.....19
Zaldivar RS.....97